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JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

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BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 5152, WEEKLY, PRICE 3/-

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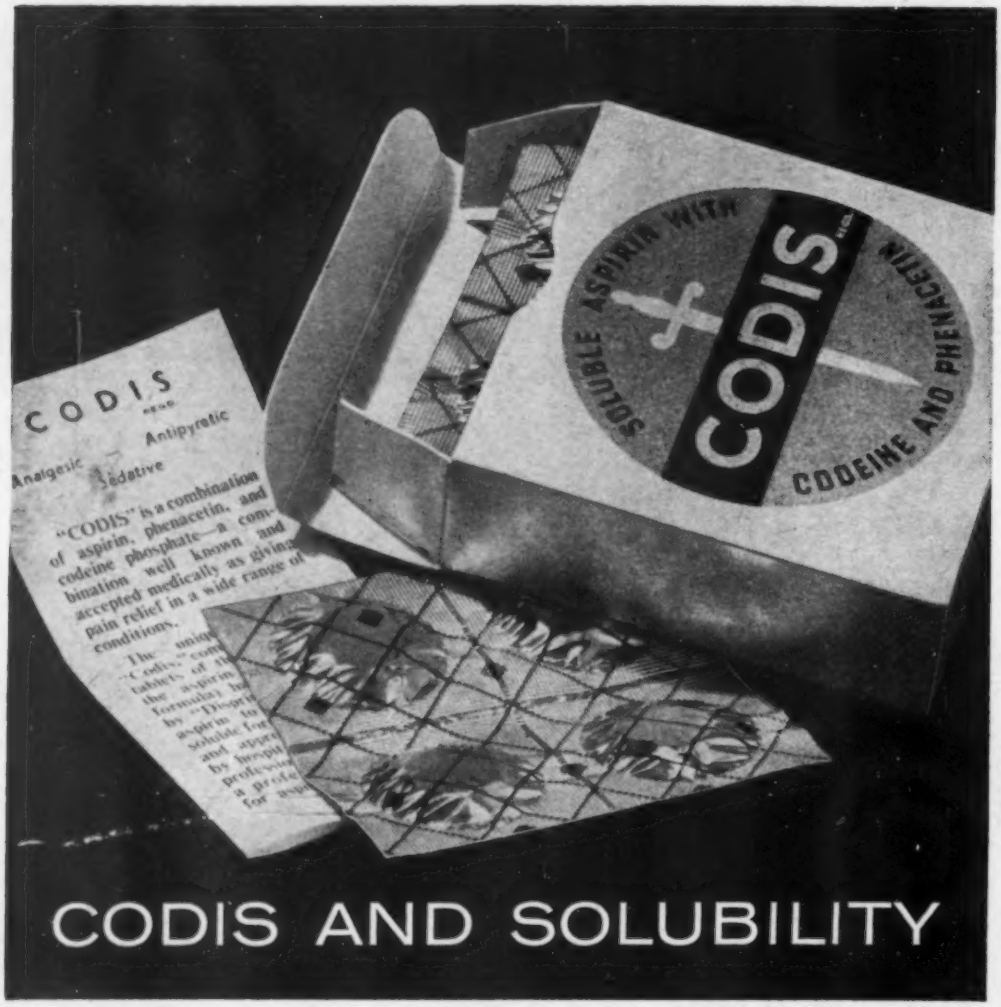
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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 3 1959

IMMUNOLOGICAL RESPONSE TO TRIVALENT ORAL POLIOMYELITIS VACCINE

BY

HERALD R. COX, Sc.D., VICTOR J. CABASSO, Sc.D., FLOYD S. MARKHAM, Ph.D., MAX J. MOSES, M.D., ARDEN W. MOYER, Ph.D., MANUEL ROCA-GARCIA, M.D., AND JAMES M. RUEGSEGGER, M.D.

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A survey of the literature to date on feeding living attenuated polioviruses for the immunization of man reveals that relatively little has been reported on simultaneous feeding of the three types of virus or the use of mixtures of them as a trivalent vaccine. This is apparently due to the fact that certain strains of poliovirus were found to interfere with the establishment and multiplication of other type strains in the human gut. Thus, Koprowski (1955) reported that type I, SM virus, interfered with the immunizing effect of type II, TN strain, when the two were fed simultaneously. In a subsequent study Koprowski *et al.* (1956) attempted to overcome this interference by feeding much larger doses of type II virus in a mixture with type I. Again interference was found to occur between the two types, though, under the conditions of the latter study, type I strain was not always dominant.

In 1955 Sabin stated that simultaneous feeding of approximately 10 million tissue-culture 50%-infective doses (TCD_{50}) of attenuated polioviruses of all three types to chimpanzees completely suppressed the multiplication and immunizing effect of only type III virus. In 1956 Sabin reported that when he fed approximately one million TCD_{50} of the naturally occurring attenuated strains (P 2149, P 712, and Glenn) simultaneously, he found no significant interference in four volunteers fed a mixture of types I and II, nor in three volunteers fed a mixture of types I and III, nor in three persons fed types II and III, nor in one person fed all three types together. He did note that, in some of the individuals fed, the appearance of antibodies was delayed and titres were in the lower range. In later studies carried out with his "optimum single plaque" strains, Sabin (1957) reported that the type II strain was the dominant one and that quite often, though not always, it interfered with the multiplication of the other two types when fed as a mixture. This finding prompted him to state that "immunization against all three types of poliovirus by a single administration of a mixture of them is not feasible" (Sabin, 1958). He therefore recommended that his three "optimal" strains be fed separately at intervals of three weeks in the order of types I, III, and II.

In contrast to some of the above findings Smorodintsev *et al.* (1959), working with some of Sabin's earlier strain variants (type I, LS of 22/12/55; type II, P 712-10ab of 5/9/56; and type III, Leon 14ab of 5/4/56), have reported a single experiment in which a trivalent vaccine containing one million TCD_{50} (a mixture of equal volumes of monovalent strains) was fed to eight staff members of the Institute's Virology Department* and to 29 children, 7 to 15 years old. No comments are made about the serological results obtained in the eight staff members, but the children with low or medium antibody levels before immunization showed "an increase in antibodies to all three types of virus."

Our interest in the possibility of using a trivalent vaccine for simultaneous immunization of humans against all three types of poliomyelitis by a single feeding was renewed about a year ago, when one of us (M. R.-G.) found that it was possible to maintain a mixed infection of types II and III polioviruses for at least 20 serial passages in monkey-kidney-tissue culture. Both types of virus were present in the stool specimen of a Minnesota child who had been fed the Lederle strains of attenuated polioviruses (Roca-Garcia, unpublished observations). This observation suggested that it might be possible to immunize against the three types of poliomyelitis by feeding the Lederle strains either in the form of capsules taken simultaneously or as a mixture in a stabilized fluid preparation, and a number of studies were initiated. Other studies in this connexion will be reported independently.

This paper presents results obtained to date in feeding different dosages of a liquid, trivalent, oral poliomyelitis vaccine to approximately 550 persons—principally employees of Lederle Laboratories, Pearl River, New York, who voluntarily requested the vaccination, and, in a few cases, members of their immediate families. All these individuals live in a semi-urban area located within approximately a 15-mile radius of Pearl River, New York, chiefly Bergen County (northern New Jersey) and Rockland County (southern New York). The study was well controlled, since all persons involved

*Institute of Experimental Medicine, U.S.S.R. Academy of Medical Sciences, Leningrad.

had ready access to the Medical Department of Lederle Laboratories, so that a good history and follow-up was obtainable in each case. The data presented here consist of the results of a serological study carried out on 241 persons out of the 550 fed; the serological studies of the remaining 309 vaccinated individuals are not yet completed, and will be reported at a later date.

Clinical Observations

Even though a very careful follow-up was made, only 3 of the 550 persons who were fed reported any clinical signs of illness during the observation period of more than two months. At the time of the second bleeding one individual reported that on the seventh or eighth day after ingestion of the vaccine she had a rather severe headache, associated with stiffness of the neck, lasting for approximately 24 hours. During this time she felt flushed, but remained afebrile and had no sore throat. This condition cleared up spontaneously, rather abruptly, and no further sequelae have been reported. Serological testing revealed this person to have been a triple negative before vaccination and to have responded to types I and III polioviruses.

The second and third patients experienced diarrhoea which lasted for a day or two during the third and fourth week, respectively, following ingestion of the oral vaccine. Since a diarrhoeal condition was being reported frequently in unvaccinated subjects in the community, it is believed that these latter cases should be completely dismissed from association with the vaccine.

Laboratory Data

Materials and Methods

Strains of Virus.—The viruses used in this study were the Lederle strains SM (type I), MEF_1 (type II), and Fox (type III) isolate #P 1149. These are the same strains which were used previously in studies carried out in Minnesota, Colombia, Uruguay, Cuba, and Finland. The properties and behaviour of these strains are now being reported separately by Cabasso *et al.* (1959).

Neutralization Tests.—Neutralization tests were carried out on the pre- and post-vaccination sera simultaneously, using the *p*H or colour method according to the procedure of Salk, *et al.* (1954). All sera were first inactivated for 30 minutes at 56° C. in a constant-temperature water-bath. The serum samples were then prepared in fourfold dilutions in duplicate, using 0.25 ml. per dilution. Approximately 100 to 300 TCD_{50} of the representative strains of virus per 0.25 ml. were added to the respective serum dilutions, and the mixtures were held at room temperature for three hours. Trypsinized monkey-kidney-tissue cell suspensions containing approximately 600,000 cells per 0.25 ml. were then added to each of the serum–virus mixtures, along with appropriate controls, and the tubes then were held at 37° C. until the sixth or seventh day, when they were read. Antibody titres were calculated by the method of Reed and Muench (1938).

Results

Results of the first experiment, using a liquid trivalent vaccine, carried out on two individuals in June, 1958, are shown in Table I (subjects 1 and 2). Subject 1 was a triple negative (no antibodies against any of the three types of poliovirus). Subject 2 showed no antibodies against two types of poliovirus (I and II). Titration of the post-vaccination sera, obtained approximately three months later, indicated that both individuals responded well to the vaccine, as shown by the antibody levels attained against all three types of poliovirus. Further, it is seen from the results obtained on the blood sample taken in March, 1959, from Subject 2 that these antibodies persisted for at least nine months. Each of these individuals was fed liquid vaccine consisting of equal volumes of each of the three types of poliovirus, and the dosage was approximately $10^{5.5}$ (300,000) TCD_{50} of each type of virus.

TABLE I.—*Antibody Response of 10 Persons Fed 0.5 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{5.5}$ TCD_{50} Each Type Virus Per Dose)*

Subject	Age in Years	Vaccine Fed	Bleeding-Date	Antibody Titres Type I	Type II	Type III
1	24	*	12/6/58	<1:4	<1:4	<1:4
			13/9/58	1:512	1:256	1:64
2	36	*	12/6/58	<1:4	1:512	<1:4
			12/9/58	1:256	>1:1024	1:32
			4/3/59	1:512	>1:1024	>1:1024
3	12	7-1238-801†	28/11/58	<1:4	<1:4	1:32
			3/2/59	1:128	1:8	1:512
4	18	,,	28/11/58	1:32	1:128	1:8
			3/2/59	1:512	1:512	1:128
5	29	,,	28/11/58	<1:4	<1:4	1:512
			29/1/59	1:32	1:128	>1:1024
6	29	,,	28/11/58	1:512	<1:4	<1:4
			21/1/59	>1:1024	<1:4	1:128
7	29	,,	28/11/58	<1:4	1:8	<1:4
			21/1/59	1:128	1:32	1:8
8	5	,,	13/1/59	<1:4	1:128	1:8
			15/2/59	1:32	>1:1024	>1:1024
9	10	,,	13/1/59	<1:4	1:512	1:8
			15/2/59	1:128	>1:1024	1:512
10	13	,,	13/1/59	1:512	1:512	1:32
			15/2/59	1:512	1:512	1:512

* A mixture of equal volumes of type I (7–1231–121), type II (7–1232–216), and type III (7–1233–318).
† A mixture of equal volumes of type I (7–1231–115), type II (7–1232–217), and type III (7–1233–319).

TABLE II.—*Pre- and Post-vaccination Status of 8 Antibody Negatives Among 10 Persons Fed 0.5 ml. Trivalent Oral Poliomyelitis Vaccine ($10^{5.5}$ TCD_{50} Each Type Virus Per Dose)*

Status of Subjects	Negative for Types	Age in Years	Post-vaccination Results Negative for Types
Triple negative 1	I II III	24	0
Double negative 5			
2	I II	12, 29	0
1	II III	29	II
2	I III	29, 36	0
Single negative 2	I	5, 10	0
Total: 8	Sum total all negatives: pre- 15; post- 1		

Eight additional persons were fed a second preparation of liquid trivalent vaccine bearing the Lot No. 7-1238-801 and containing approximately $10^{5.5}$ (300,000) TCD_{50} of each type virus per 0.5 ml. This vaccine has been used for all the additional trials reported in this paper. From data presented in Tables I and II it is seen that a good antibody response was induced by the 0.5-ml. dose of vaccine in all but one of the individuals. These include one person who was a triple negative, two who were double negatives for types I and II, one who was a double negative for types II and III, two who were double negatives for types I and III, and two additional persons who were negative for type I.

After feeding the trivalent vaccine, only one person was left without demonstrable antibodies to any one of the three types of poliovirus (see Table II). Prior to vaccination this individual had been a double negative for types II and III polioviruses. He apparently failed

to respond to the type II component of the vaccine. No persons were left as double or triple negatives after being fed the trivalent preparation.

Table III shows the results obtained in a single individual, 38 years old, who first was fed capsules containing approximately 10^5 (100,000) TCD_{50} of each of the three types of poliovirus at three-week intervals. This man, who had no antibodies against types II and III polioviruses, failed to get an immune response following this feeding procedure. Subsequently, in November, 1958, he was fed a 0.5-ml. dose of liquid trivalent vaccine, and again he failed to show a demonstrable serological response. Finally, in January, 1959, he was fed a 2-ml. dose of the same liquid vaccine which contained approximately $10^{6.1}$ (1,200,000) TCD_{50} of each of the three poliovirus strains. Titration of the serum sample taken on February 11, 1959, showed a good serological response for all three types of polioviruses; antibody titres were 1:1024 for type I; 1:512 for type II; and 1:32 for type III.

TABLE III.—*Antibody Pattern of an Adult After the Feeding of Different Dosages of Oral Poliomyelitis Vaccine (Dr. A. T., 38 years)*

Vaccine	Material Fed	Virus Titre of Vaccine	Pre- or Post-feeding	Bleeding-date	Antibody Titre†		
					Type I	Type II	Type III
Each of the 3 polio types at 3-week intervals	Capsules	10^5 TCD_{50} per capsule	Pre-	9/9/58	32	<4	<4
			Post-	20/10/58	64	<4	<4
0·5 ml. trivalent ⌀7–1238–801*	Liquid	$10^{5.5}$ TCD_{50} each virus type	Pre-	19/11/58	128	<4	<4
			Post-	19/12/58	128	<4	<4
2 ml. trivalent ⌀7–1238–801	,,	$10^{6.1}$ TCD_{50} each virus type	Pre-	5/1/59	128	<4	<4
			Post-	11/2/59	1024	512	32

* ⌀7–1238–801 = equal volumes of type I (⌀7–1231–115), type II (⌀7–1232–217), and type III (⌀7–1233–319).
† Reciprocal of the serum dilution.

Following these encouraging results, a comparative study was set up in which one group of patients received a 1-ml. dose of trivalent vaccine representing $10^{5.8}$ (600,000) TCD_{50} of each strain of poliovirus while a second group received a 2-ml. dose representing $10^{6.1}$ (1,200,000) TCD_{50} of each type. Table IV, Charts 1, 2, and 3, and Fig. 1 summarize the data which were obtained on the 42 subjects who received the 1-ml. dose of trivalent vaccine, Lot No. 7-1238-801. The volunteers ranged in age from 8 to 65 years, with the majority between the ages of 11 and 50. Among this group were one triple negative, two double negatives for types I and II, one double negative for types II and III, three double negatives for types I and III, a single negative for type I, five single negatives for type II, and three single negatives for type III. Thus there were 16 persons showing a total of 24 "negatives" for all three types of poliovirus.

TABLE IV.—*Pre- and Post-vaccination Status of 16 Antibody Negatives Among 42 Persons Fed 1 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{5.8}$ TCD_{50} Each Type Virus Per Dose)*

Pre-vaccination Antibody Negatives		Post-vaccination Status			
Negative to Type	No. of Subjects	Negative to Type			Converted
		I	II	III	
I, II, III	1			1	
I, II	2				2
I, III	3	1			2
II, III	1				1
I	1	1			
II	5		3		2
III	3			1	2
Total	16	2	3	2	9

Sum totals all negatives, pre- 24; post- 7.

Table IV also gives the post-vaccination antibody pattern of these 42 persons approximately 30 days after ingestion of the 1-ml. dose of trivalent vaccine. Note that no triple or double negatives remained after vaccination and only seven persons were left as single negatives for any of the three types of poliovirus. One of these subjects remained without antibody to type I; he previously had been a double negative for types I and III. A second individual, originally a single negative to type I, was left without antibodies to type I. Three persons, previously negative to type II virus only, were still without antibodies to this type virus. One individual who had been a triple negative was left without antibodies to type III virus only, and one individual who previously was a single negative for type III virus did not respond to the type III component of the triple vaccine. For detailed information concerning individuals who were fed the trivalent vaccine see Charts 1, 2, and 3, which depict the antibody response of these 42 persons to types I, II, and III polioviruses, respectively.

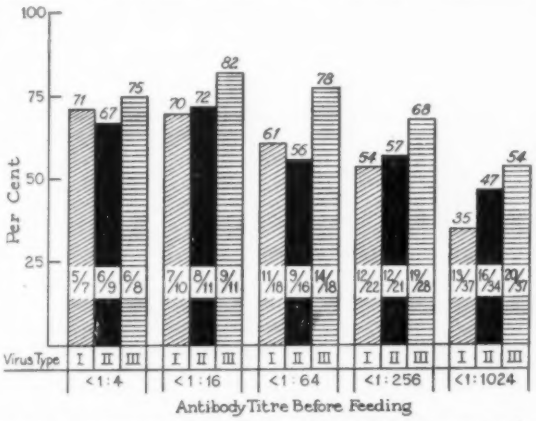

FIG. 1.—Percentage of 42 persons with fourfold or greater antibody rise following feeding of 1 ml. of trivalent oral poliomyelitis vaccine ($10^{5.8}$ TCD_{50} of each type of virus per dose).

Fig. 1 shows the number and percentage of persons who manifested a fourfold or greater antibody rise after the feeding of the 1-ml. dose of trivalent vaccine. While the numbers are small, it is seen from this figure that, of those individuals with pre-feeding antibody titres of <1:4, 71% responded to type I, 67% to type II, and 75% to type III. Of those with antibody titres of <1:16 either a primary or a booster response was shown by 70% to type I, 72% to type II, and 82% to type III. As would be expected, a decreasing proportion of those persons with greater initial antibody titres manifested a response, but even of those persons showing initial antibody titres <1:1024, 35% showed either a primary or a booster effect to type I, 47% to type II, and 54% to type III.

Pre-feeding	Post-feeding: <1:4	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	>1:1024	Total No. Fed	No. with Fourfold or Greater Response
<1:4	2				4		1					7	5
1:4			1									1	0
1:8							1	1				2	2
1:16				1	1						1	3	1
1:32					1	1		1	1	1		5	3
1:64						1						1	0
1:128							2			1		3	1
1:256							1	5	2	1		9	1
1:512								1	4	1		6	0
1:1024									1			1	
>1:1024											4	4	
Totals	2	0	1	1	6	2	5	8	8	4	5	42	13

CHART 1.—Poliovirus Type I Antibody Response of 42 Persons Fed 1 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{5.5}$ TCD_{50} of Each Type per Dose)

Pre-feeding	Post-feeding: <1:4	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	>1:1024	Total No. Fed	No. with Fourfold or Greater Response
<1:4	3	3	1		1				1			9	6
1:4									1			1	1
1:8									1			1	1
1:16				1	1							2	0
1:32				1	1					1		3	1
1:64											1	1	1
1:128							1	1	1		1	4	2
1:256							1	2	1			4	0
1:512								1	3	1	4	9	4
1:1024										1	1	2	
>1:1024									1		5	6	
Totals	3	3	1	2	3	0	2	4	9	3	12	42	16

CHART 2.—Poliovirus Type II Antibody Response of 42 Persons Fed 1 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{5.4}$ TCD_{50} of Each Type per Dose)

Pre-feeding	Post-feeding: <1:4	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	>1:1024	Total No. Fed	No. with Fourfold or Greater Response
<1:4	2	1	2		2				1			8	6
1:4				1								1	1
1:8							1	1				2	2
1:16					2			1			1	4	2
1:32							1		1	1		3	3
1:64								1			1	2	2
1:128							3	2	2		1	8	3
1:256							3	1				4	0
1:512									3	1	1	5	1
1:1024										2		2	
>1:1024										1	2	3	
Totals	2	1	2	1	4	0	8	6	7	5	6	42	20

CHART 3.—Poliovirus Type III Antibody Response of 42 Persons Fed 1 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{5.5}$ TCD_{50} of Each Type per Dose)

The response among these volunteers should be compared with that obtained in 188 volunteers fed the 2-ml. dose of the same vaccine, which represents $10^{6.1}$ (1,200,000) TCD_{50} of each type virus per dose (see Table V and Charts 4, 5, and 6). The age range of the 188 persons was from 4 to 60 years, with the greatest numbers ranging from 21 to 50. In this group there were 11 triple negatives (aged 18 to 44); 18 double negatives to types I and II (17 to 39); 7 double negatives to types II and III (19 to 38); and 10 double negatives to types I and III (23 to 54). There were 14 single negatives to type I poliovirus (20 to 50); 6 single negatives to type II (22 to 39); and 30 single negatives to type III (10 to 58). Thus there were 96 persons showing a total of 153 "negatives" for all three types of poliovirus. Results when the sera of these same individuals were tested about 30 days after taking 2 ml. of the trivalent vaccine are shown in Table V. No triple or double negatives and only 11 single negatives remained. Two individuals were still negative to type I; nine were left negative to type II; and none remained negative to type III.

The pre-vaccination status of those who failed to show an antibody response to the triple vaccine is presented in the left-hand column of Table V. One of the persons left without antibody to type I had been a single negative to type I. The second individual left without antibody to type I had been a double negative to types I and III. One of the subjects who remained negative to type II had been a single negative to type II. Another person left without type II antibody had been a type II and III double negative.

In addition, three persons who were originally type I and II double negatives and four persons who were triple negatives were left without type II antibody. Charts 4, 5, and 6 show the antibody response of the 188 persons fed the 2-ml. dose of the trivalent vaccine to types I, II, and III polioviruses.

A summary of antibody conversion effect as well as booster response of the 188 persons fed 2 ml. of vaccine is shown in Fig. 2. Of those individuals with antibody titres originally <1:4, 96% responded with antibodies to type I, 78% to type II, and 100% to type III. Likewise, of all individuals who showed pre-vaccination antibody titres of <1:16, 90% showed either a primary or booster effect to type I, 83% to type II, and 95% to type III. Corresponding primary or booster effects are shown for those groups of individuals whose initial antibody titres were <1:64, <1:256, or <:1024. It is remarkable that of all persons who showed initial antibody titres <1:1024, 62% showed either a primary or a booster response to type I, 67% to type II, and 71% to type III.

Discussion

From the above results it is apparent that a much better neutralizing antibody response was obtained in individuals fed the 2-ml. dose of trivalent poliovirus vaccine than in those receiving the 1-ml. dose. While the results obtained with the 0.5-ml. dose are good, it must be admitted that the number of people involved is small, It is important that these highly favourable results were obtained primarily in adults. We believe that this should be noted, because the study carried out in Minnesota in 1958 clearly showed that children could be more

Pre-feeding	Antibody Titres: Post-feeding											Total No. Fed	No. with Fourfold or Greater Response
	<1:4	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	>1:1024		
<1:4	2	2	9	5	10	5	12	1	7			53	51
1:4							1		1			2	2
1:8			2	3	1		2	2	2			12	7
1:16					1			2		1		4	3
1:32					2	5	6	3	4	1		21	14
1:64						1	5	2	1	1	3	13	7
1:128					1	2	10	9	10	2	2	36	14
1:256								5	5	1	2	13	3
1:512								2	8	3	5	18	5
1:1024									1	7	4	12	
>1:1024											4	4	
Totals	2	2	11	8	15	13	36	26	39	16	20	188	106

CHART 4.—Poliovirus Type I Antibody Response of 188 Persons Fed 2 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{6.1}$ TCD_{50} of Each Type per Dose)

Pre-feeding	Antibody Titres: Post-feeding											Total No. Fed	No. with Fourfold or Greater Response
	<1:4	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	>1:1024		
<1:4	9	5	6	4	2	2	7	3	2	1	1	42	33
1:4							1	1	1			3	3
1:8			1		4	1		3	3	1	2	15	14
1:16			1		1		1	1	3		1	8	6
1:32					3	1	3	3	2	2		14	10
1:64						1	4		1	1	3	10	5
1:128						1	11	4	6		7	29	13
1:256								3	3	1	5	12	6
1:512									6	3	14	23	14
1:1024									3	2	10	15	
>1 1024										3	14	17	
Totals	9	5	8	4	10	6	27	18	30	14	57	188	104

CHART 5.—Poliovirus Type II Antibody Response of 188 Persons Fed 2 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{6.1}$ TCD_{50} of Each Type per Dose)

Pre-feeding	Antibody Titres: Post-feeding											Total No. Fed	No. with Fourfold or Greater Response
	<1:4	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1024	>1:1024		
<1:4		2	8	13	17	5	6	3	2	1	1	58	58
1:4			1									1	0
1:8			1	2	5		2	1	3			14	11
1:16				1	1	2	2	3	4			13	11
1:32					3	5	5		4	4	3	24	16
1:64					1	2	5	1	3		3	15	7
1:128							6	2	10	1	3	22	14
1:256								3	4		4	11	4
1:512									8	4	5	17	5
1:1024									1	3	2	6	
>1:1024										1	6	7	
Totals	0	2	10	16	27	14	26	13	39	14	27	188	126

CHART 6.—Poliovirus Type III Antibody Response of 188 Persons Fed 2 ml. of Trivalent Oral Poliomyelitis Vaccine ($10^{6.1}$ TCD_{50} of Each Type per Dose)

readily immunized with the oral vaccine than could adults (Barr *et al.*, 1959). That is one of the reasons why the decision was made to use adults primarily in carrying out the study with the trivalent vaccine reported here.

It is obvious, of course, that from the standpoint of ease and cost of administration a trivalent oral vaccine has many advantages to offer over the procedure of feeding the three virus strains separately. There is no doubt that a trivalent oral vaccine would be of great advantage to public-health workers, who ordinarily have limited time and funds with which to carry out mass-immunization programmes.

TABLE V.—*Pre- and Post-vaccination Status of 96 Antibody Negatives Among 188 Persons Fed 2 ml. of Trivalent Oral Poliomyelitis Vaccine* ($10^{6.1}$ TCD_{50} *Each Type Virus Per Dose*)

Pre-vaccination Antibody Negatives		Post-vaccination Status			
Negative to Type	No. of Subjects	Negative to Type			Converted
		I	II	III	
I, II, III	11		4		7
I, II	18		3		15
I, III	10	1			9
II, III	7		1		6
I	14	1			13
II	6		1		5
III	30				30
Total	96	2	9	0	85

Sum total all negatives, pre- 153; post- 11.

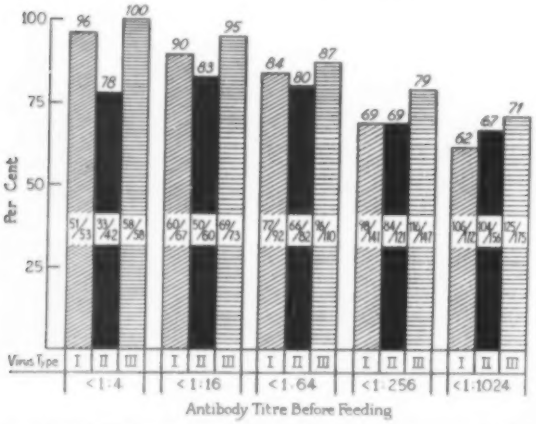

FIG. 2.—Percentage of 188 persons with fourfold or greater antibody rise following feeding of 2 ml. of trivalent oral poliomyelitis vaccine ($10^{6.1}$ TCD_{50} of each type of virus per dose).

It is of interest to note that the percentage of persons responding to the trivalent vaccine appeared to be highest for types III and I and somewhat less for type II. From the frequency of the serotypes of virus seen in the disease as it is encountered under natural conditions, a lesser response to type II would represent the least degree of risk. All knowledge to date, of course, indicates that the most important type to protect against is type I, followed probably by types III and II in that order. Certainly use of the trivalent vaccine as reported here gave excellent results in immunizing against types I and III, and, though the rate of response to type II was not as good, it is nevertheless encouraging, inasmuch as these results were obtained by feeding adults a single 2-ml. dose.

It must be pointed out also that in this study the vaccine was fed at various times of the day and no special effort was made to determine if a better rate of response could be obtained by feeding the vaccine under more nearly optimal conditions, such as before or after meals. Perhaps feeding the vaccine after a meal, at which time the gastric acidity could be partially reduced by food, might give better results. Perhaps an even higher rate of response could be obtained by giving a second dose of trivalent vaccine at a later interval, such as six to eight weeks after the administration of the first dose. Such a procedure might fill in the "negative gaps" among those individuals who failed to respond to the first feeding.

These problems are being explored at the present time.

Finally, similar studies are now under way with trivalent vaccines prepared from sub-line strains derived from the strains of poliovirus discussed here. These particular sub-line strains show less neurotropic activity in monkeys, and their immunogenicity for man is under investigation. In any event, there seems to be little doubt that by using the strains of poliovirus reported here it is entirely possible to induce in adults, and presumably in children also, a high state of immunity to all three types of poliovirus by a single feeding of trivalent oral poliomyelitis vaccine.

Summary and Conclusions

To date a serological study has been completed on 241 paired sera obtained from 550 volunteers fed various dosages of a liquid trivalent poliovirus vaccine. The majority of subjects in the study were employees of Lederle Laboratories, American Cyanamid Company, or their immediate families, and all resided in a semi-urban area within a 15-mile radius of Pearl River, N.Y.

Good neutralizing antibody responses, as judged by primary conversions or a titre increase of at least fourfold, were elicited when each of the three types of virus was present in the mixture at concentrations of $10^{5.5}$ (300,000), $10^{5.8}$ (600,000), and $10^{6.1}$ (1,200,000) TCD_{50}. The most favourable results, however, were obtained in the group of 188 persons fed the largest dose—namely, $10^{6.1}$ (1,200,000) TCD_{50} of each of the three types of poliovirus in 2 ml. of vaccine. Prior to vaccination with the single oral dose of vaccine this group of 188 persons included 11 triple negatives, 35 double negatives, and 50 single negatives. After vaccination, no double or triple negatives and only 11 single negatives remained. The conversion rate, therefore, was 93%. Two persons were left without antibodies to type I, and nine without antibodies to type II, while none was left without antibodies to type III.

These results indicate that it is both feasible and practicable to immunize against all three types of poliovirus by a single feeding of a trivalent oral poliovirus vaccine. The advantages of this type of vaccine are discussed.

We wish to express our appreciation to Mrs. Henrietta Nozell and her associates, Mrs. Evelyn Hunter, Mrs. Hilda Salino, Mr. Terrence James, Mr. Robert McRae, and Mr. Ronald Pitt for the serological studies. We also thank Mrs. Elisabeth Manoogian and Mrs. Esther Chasan for their help in preparation of the manuscript.

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ACRYLIC INVESTMENT OF INTRACRANIAL ANEURYSMS

BY

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My original intimation of this subject was presented to give preliminary notification of a new method of treating bleeding intracranial aneurysms (Dutton, 1956), unsuitable for clipping or ligation, and previously considered manageable only by the uncertain method of muscle wrapping. Logue (1956) comments thus: ". . . surrounding the sac wall with a coat of hammered muscle to support it from the outside, a procedure which surely must have more effect on the surgeon's peace of mind than on the aneurysm." He also notes in 9% of his cases "contraindications to surgery" due to "anomalies of the anterior part of the circle of Willis, so that both anterior cerebral arteries arise from one internal carotid trunk, with the result that occlusion of the anterior cerebral is not feasible." Hook and Norlén (1958) wrapped 8 out of an operative series of 57 middle cerebral aneurysms.

The passage of time has allowed of the addition of further cases for study, and this paper contains an appraisal of this method consequent on a three-year follow-up. Certain additional advantages are also discussed, especially in relation to accidental rupture during surgical operation. Details of experimental work and aseptic techniques are also presented.

Experimental Work

The method was originally developed to provide an immediate unyielding investment for the sac and parent vessels. "Simplex rapid" cold curing acrylic made by Dental Fillings Limited was finally selected, because its physical properties were most suitable, and though certain drawbacks were known (Lefkowitz *et al.*, 1949; Zander, 1951; Kramer and McLean, 1952; Coy *et al.*, 1952; van Huysen and Boyd, 1953; Müller and Maeglin, 1953; Massler and Silberkweit, 1954; Nygaard-Östby, 1955; Kramer, 1955, 1956), relating to the use of "self-curing" acrylics in experimental dental caries, its use was thought to be practicable. This material was known to withstand immersion in salinous fluids for long periods, to set with a smooth surface, to show minimal shrinkage only during polymerization of the order of 6% by volume, corresponding to approximately 2.7% linear, and investigations on heat production revealed that small quantities—that is, 1–2 ml.—when allowed to polymerize, reached 115° F. (46.1° C.). With intracranial use such temperature production was thought to be of small moment, especially in the presence of cerebrospinal fluid and saline wash. The problem of incomplete polymerization, amounting to between 1% and 5%, was also considered to be amenable to the same method of dissipation.

In vivo experiments were then conducted, goats being found entirely suitable. Initially, collars of acrylic were made around peripheral limb vessels, and the immediate, early, and late results noted. There were no immediate effects on the vessel or limb circulation, no infection or foreign-body reaction, the collar was well accepted by the host; and, most important, there was no encystment, the collar being firmly felted. Segments of the vessel and collar were studied, and histologically the intima was found to be healthy, the media was normal, and fibrosis of the adventitia was found to be not great. There was no sign whatsoever of thrombus deposition in the vessel.

Acrylic and bone-wax (as control) implants and vessel investments were then made into the cerebral sulci of goats, to study the immediate and delayed vascular and cellular effects. Specimens were examined at varying post-implant periods ranging from seven days to seven weeks. Two blocks of cortex removed after seven days were frozen and stained for nerve-cell bodies (carbol azure) and for lipoid (scharlach R and haematoxylin). In a few sections from one block a narrow wedge-shaped zone of increased cellularity was seen around one of the small cortical vessels, which passed through the nerve-cell layer into the subcortical white matter. No other sign of damage to the brain underlying the implanted material (acrylic) was found. In a control block from the same animal in which bone wax had been inserted a similar zone of perivascular reaction was seen. Here the course of the vessel was similarly marked out by macrophage cells containing granules of neutral fat.

Blocks of cortex removed seven weeks later were also examined. In all, the molecular layer of the cortex showed increased cellularity (Figs. 1 and 2) below the site of insertion. In this situation a mild proliferation of astrocytes had occurred accompanied by an increase in the number of microglial cells, the processes of which were often slightly swollen and could be visualized in ordinary nerve-cell preparations. At one point the superficial part of the grey matter showed a slight increase in microglial cells, but nowhere had there been any detectable destruction of neurones. The microglial cells did not contain lipoid.

Summarizing, one can say that the insertion of acrylic had produced a mild localized microglial and astrocytic reaction in the molecular layer of the cortex, but its presence had not proved detrimental in any way to the underlying nerve cells. The narrow wedge-shaped areas of perivascular damage are to be regarded as the consequence of the surgical procedure and cannot be directly related to the effect of the acrylic, since similar appearances were seen in the control sections.

Bacteriology, with Special Reference to Cobalt Irradiation

The powder (polymer) as received from the manufacturers is probably sterile; all tested specimens have failed to produce any organisms, but contamination is easily effected, and the addition of monomer to effect

polymerization is no guarantee that sterility will be preserved. The monomer certainly exerts some bacteriostatic influence on bacteria, but it does not destroy them. The polymerized acrylic is porous, and infected material has the ability to contaminate tissues. When staphylococci of a known strain were added to monomer, polymer, or polymerizing paste and then moulded into a cuff around a rolled tube of sterile filter paper, culture of the latter in broth revealed a heavy growth. Robinson and Macalister (1954) reproduced these findings in animal experiments.

Originally, autoclaving of the powder was advocated, but experience soon proved that any period in excess of five minutes proportionately destroyed the benzoyl peroxide and polymerization was then delayed. Autoclaving for 20 minutes caused the reaction to be delayed as long as 24 hours. An alternative method of sterilization was thus required, and one which would not interfere with the activator systems or adversely affect the physical properties. I am indebted to Dr. Tudway, of Bristol General Hospital, for the treatment of the polymer with 2 to 3 million rads by means of cobalt radiation. The powder was placed in a special "perspex" container and submitted to radiation from radioactive cobalt during two successive nights, from 5 p.m. till 9 a.m. Previous heavy contamination with organisms including sporebearers was completely destroyed. Control non-irradiated specimens gave heavy growths. Polymerization was completely unaffected. Sterilization of the monomer was easily effected by means of a pressure Seitz filter, and it was then sealed in sterile ampoules.

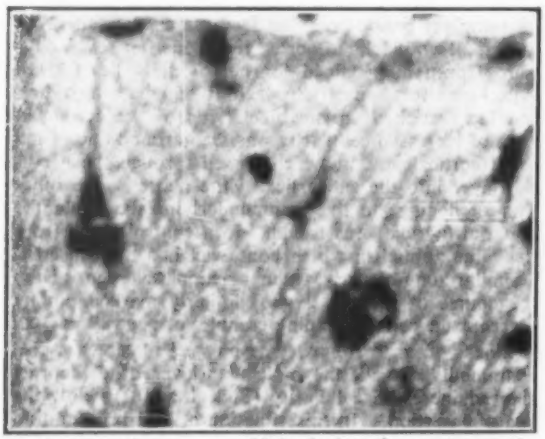

FIG. 1.—Normal appearance. Molecular layer from cortex remote from operation site, normal cell density. (Carbol azure. ×360.)

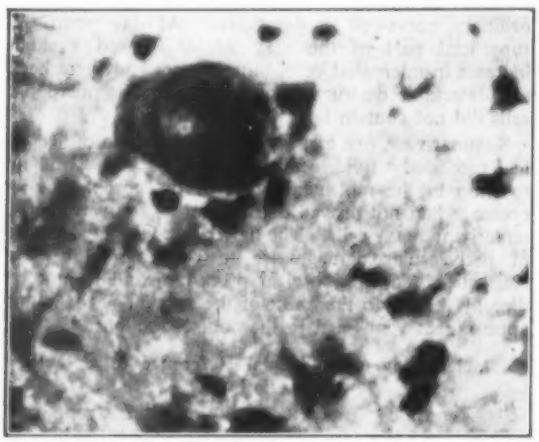

FIG. 2.—High-power view of the proliferated astrocytes and microglial cells of the affected molecular layer. (Carbol azure. ×240.) (Preparation by Dr. R. M. Norman.)

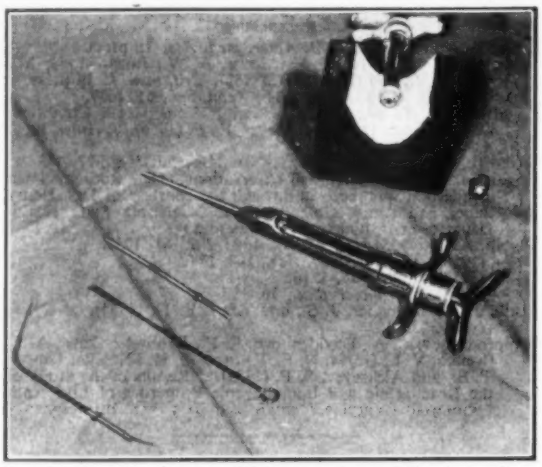

FIG. 3.—Dental syringe modified with a large drill-hole so that a large-bore needle can be introduced, the distal end being blunt. The curved needle may also be of value in getting into difficult areas.

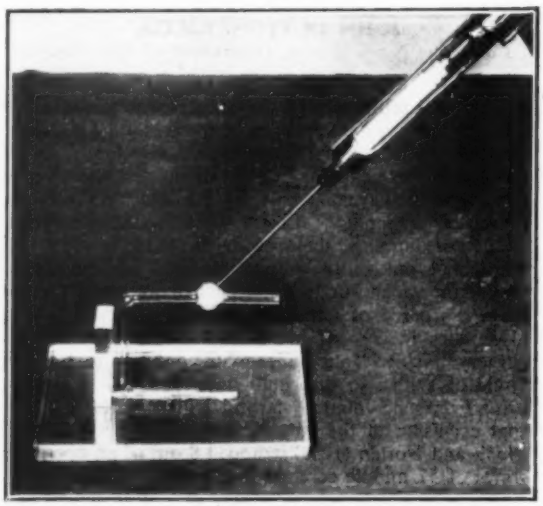

FIG. 4.—After vigorously shaking the cartridge the material slowly gels in three minutes, and during this time it is suitable for injection through the cannula. The illustration shows a model aneurysm being invested.

The Method

Sterile polymer is put up into sterile empty dental anaesthetic cartridges. The monomer is introduced by needle puncture of the cap of the cartridge, a proportion of three of polymer to one of monomer being roughly correct. Vigorous shaking promotes an even mix, and when the consistency is that of thick cream it is ready for application. About three minutes is required to this stage—the material quickly becomes too thick to pass the wide-bore cannula—and polymerization is "completed" in about a further five minutes, the material being quite firm. At the thick-cream stage it

flows around the vessel and sac, forming a collar, and can be moulded by means of a gutta-percha "sling" (Figs. 3 and 4).

Review of Cases

All the cases were of subarachnoid haemorrhage requiring surgical intervention in which the angiographic investigation suggested the impossibility or technical difficulty of ligation or clipping, either proximal or of the neck of the aneurysm (Fig. 5). Carotid ligation in the neck was thought to be suitable only in certain cases of aneurysm at the posterior communicating artery level or lower, and was never practised for aneurysms of the middle cerebral or anterior cerebral. All cases were

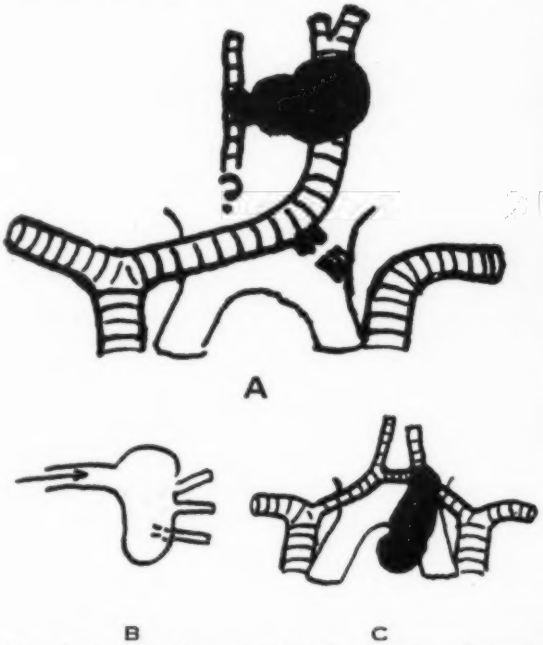

FIG. 5.—A, Anterior communicating aneurysm; abnormal vascular pattern. B, Middle cerebral aneurysm. C, Anterior cerebral aneurysm.

operated upon under general anaesthesia, respiration control being used and hypothermia being artificially induced to an average of 29.5° C. On certain occasions hypotension was artificially induced. All cases were anaesthetized by Dr. P. L. F. Mortimer, and his contribution to their success is noted and appreciated.

Whenever conventional methods of treatment were more appropriate they were invariably used, and thus in three years only 17 cases are available for study. They comprise nine cases of the anterior communicating artery and eight of the middle cerebral artery.

Aneurysms of the Anterior Communicating Artery (Nine Cases)

Case 1

A man aged 36 had his initial subarachnoid haemorrhage five weeks before admission and his second haemorrhage two weeks before. Within three days of admission he was submitted to operation, after angiograms had displayed a multilocular aneurysm of the anterior communicating artery, filling from the left anterior cerebral artery only, and with considerable spasm of the internal carotid artery proximal to its termination. At operation on January 23, 1956, the aneurysm was seen to comprise a bilobed anterior and unilobar posterior sac about the anterior communicating artery, which was supplied by a "right-sided" anterior cerebral artery taking origin from the left internal carotid. No anterior cerebral branch was evident arising from the right internal carotid, and there was no vessel representing the anterior cerebral on the left side proximal to the anterior communicating. The anatomy was thus complex, and proximal or local clipping was inapplicable. The chiasm was screened with a small sheet of gutta-percha and acrylic investment performed. Polymerization was "complete" in eight minutes, the complex sac and entrant vessels all being covered. There was no alteration in vessel calibre or brain circulation.

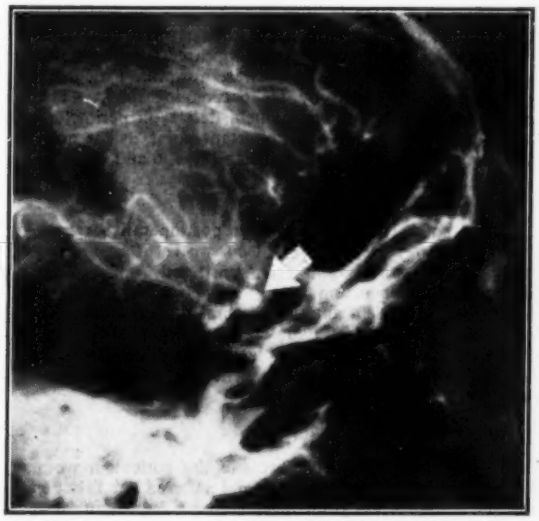

FIG. 6.—Case 1. Pre-operative left carotid arteriogram. Siphon shows slight narrowing of its calibre; a berry-shaped aneurysm is shown on the anterior cerebral artery in the midline, close to the site of origin of anterior communicating artery or possibly arising from the latter. Both anterior cerebrals fill only from the left and are centrally placed.

FIG. 7.—Case 1, after investment. Post-operative left carotid arteriogram. Compared with the previous series, the siphon and neighbouring vessels are now of normal calibre. The aneurysm is only slightly smaller. Note evidence of ventricular dilatation.

The patient, pre-operatively, was somnolent, showing signs and symptoms of raised intracranial pressure, appearing ill, with an ominous dusky suffusion. He was well immediately after the procedure, but in a few days became increasingly somnolent, apathetic, and incontinent. Then after a few more days began a slow and gradual return to superficial normality one month later, though he was somewhat disorientated and, for a period, showed a minor euphoric apathy with some impairment of normal social responsibility. One year later he was almost back to his normal (pre-haemorrhage) state. His Dundee accent was again noticeable, and he voluntered that his working capacity was about 75% of normal. He had then been back to his normal occupation as a fitter for five months. Three weeks after operation angiograms demonstrated no spasm or interruption of the vessels, the aneurysmal sac appeared much as before, though it was smaller. There was, however, a degree of hydrocephalus, revealed by air encephalography. There was no evidence of any visual field defect on perimeter or screen to white and red—an important point, as the acrylic material had lain close to the chiasm (Figs. 6 and 7).

Case 2

A man aged 31 made a prompt post-operative recovery and returned to his employment six weeks after discharge. Pre-operative angiograms demonstrated an anterior communicating aneurysm filling only from the left side, there being no evident anterior cerebral branch on the right. His first haemorrhage had occurred one week before operation, his second four days later. On admission he had a most severe and ominous headache and was in imminent danger of a third haemorrhage.

Case 3

This case was instructive because the patient, a woman aged 34, was 24 weeks pregnant and suffered her first bleed one and a half weeks prior to operation. Both mother and foetus tolerated without incident hypothermia of 30.6° C. for several hours and surgical intervention. At the beginning of the operation the spasm seen in the angiograms was noted. During dissection of the sac the fundus ruptured and haemostasis was secured by means of a Norlén clip across the body of the sac ; and the clip, the sac, and entrant vessels were then all invested with acrylic. The patient was discharged back to her original hospital after one week, and later gave birth to a normal child at full term. Parturition was complicated by haemorrhage requiring transfusion, and three and a half months later she died suddenly from acute liver atrophy, presumably secondary to homologous serum jaundice.

Examination of the specimen revealed an invested aneurysm with no sign of further haemorrhage, though there was a defect in the shell of acrylic where both anterior cerebral arteries distal to the sac emerged. The orifice for these vessels was larger than one would have wished, and it is possible that haemorrhage could at some time have occurred from this site. The sac and anterior communicating arteries were free from thrombus, and the shell of the acrylic was felted in place by a thin fibrous capsule derived from the arachnoid and was stained with haemosiderin. The infero-medial border of the right frontal lobe showed some absorption of the grey matter with two tiny areas of absorption in the underlying white matter immediately adjacent to the acrylic shell. Otherwise the brain appeared quite normal, showing no signs of infarction in the distribution of either anterior cerebral artery or elsewhere, and these findings were confirmed histologically. One of the emerging anterior cerebral arteries showed a patchy sub-intimal fibrosis, severe only in one place, the companion vessel being otherwise normal. It was thought that this subintimal proliferation was a little greater at this site than one would expect to see in a woman of 34, but there was also a great deal of thickening and change within the internal carotid artery on the left side, considerably proximal to the scene of operation or haemorrhage. No direct inferences can therefore be made from these findings save to note that the presence of the acrylic, after being in place for nine and a half months, had resulted in no gross alteration in the normal appearances of the vessels.

Cases 4-9

Four further cases progressed satisfactorily, but the next two patients subsequently died after operation, neither death being attributable apparently to the method of treatment.

Case 8.—A man aged 40 suffered his first haemorrhage three weeks and the second one three days before operation. He was somnolent, with raised intracranial pressure and a left hemiparesis prior to operation. Angiograms revealed a left anterior cerebral artery only, with considerable spasm of the internal carotid vessel and anterior cerebral on that side and a sac lying at the level of the anterior communicating artery. He progressed satisfactorily for two days post-operatively and then developed a right-sided weakness and became unresponsive. A second operation was performed, but nothing abnormal was noted apart from considerable enlargement of the gyri. He died shortly afterwards, and examination of the specimen revealed that massive cerebral oedema of uncertain origin was the cause of his demise. The sac and parent vessels were satisfactorily encased in the acrylic and there was no thrombosis.

Case 9.—A man of 55 developed a weakness of all his limbs excepting the left arm after an apparently successful operation, and died a month later, mainly from severe disturbances of metabolism with gross fluctuations of electrolyte values. At necropsy there was no thrombosis, and no evident haemorrhage from the sac since operation. It was presumed that his signs and progress post-operatively were the result of spasm or delayed thrombosis of the perforated vessels, though no marked softening could be detected.

Aneurysms of the Middle Cerebral Artery (8 Patients)

In all patients the presenting findings pre-operatively were minimal weakness and, in appropriate cases, dysphasia. All but one had bled twice, the weakness or dysphasia invariably following the second haemorrhage, for which they were referred to the neurosurgical unit. Their ages varied from 35 to 55 years, and in all cases angiograms demonstrated spasm either proximal or immediately distal to the sac. All operations were conducted under hypothermia ; and initially, as a first step, a silk thread was placed around the middle cerebral artery proximal to the immediate operation area. In each case the sac was either giving origin to a primary branch vessel or was so involved that clipping the neck was inadvisable or the neck was difficultt to define clearly without causing a rupture.

All patients recovered, the motor weakness clearing up quickly ; the speech defects were usually much later in clearing. Two patients showed prompt improvement of their speech defect immediately after recovery from the anaesthetic, and it was presumed that this was due to an immediate improvement in the circulation (Figs. 8 and 9). Pre- and post-operative electroencephalograms and angiograms suggested no disturbance to the circulation and function of the middle cerebral territory.

Recurrent Haemorrhage

To date there has been no proved case of recurrent haemorrhage in any of the survivors, and review of the necropsy reports in the two cases of aneurysm of the anterior communicating artery showed no evidence of recurrent haemorrhage. One case of the anterior communicating group required re-exploration

and frontal lobectomy because of a haemorrhagic, swollen, and necrotic area in the brain substance. This was not a case of expansion of the depths of the sulci with clot, and there was no evident communication with the aneurysmal sac. The age of the blood clot was considerable, and it was not known whether this clot had originated before the first operation or occurred subsequently.

Fig. 8.—Pre-operative left carotid arteriogram. A berry aneurysm is shown lying on the middle cerebral artery, about 1.8 cm. from its origin; the fundus is directed upwards and is lying proximal to any primary branch of the main stem.

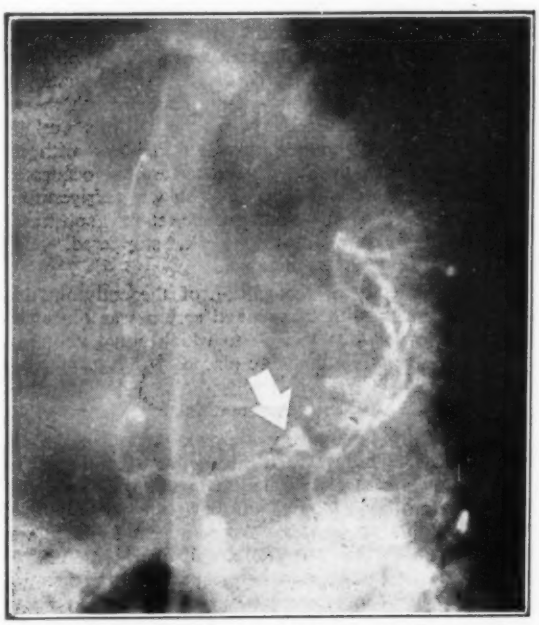

Fig. 9.—Same case as Fig. 8, after investment. Post-operative left carotid arteriogram. This is comparable with the pre-operative findings. The shift as shown on the antero-posterior view was the result of cerebral oedema and subdural hydroma which subsequently resolved.

Certain Special Points of Technique

A clear definition of the sac is required for this method to be effective. This may be a tedious procedure, and sometimes it is profitable to suck away the adjacent brain, especially if necrotic or softened with clot (Norlén and Olivecrona, 1953). The sac can be further prepared for investment by passing a thread behind the parent vessel, so that gentle traction can elevate the sac from its "bed." This allows the semi-fluid acrylic to flow around to the deep surface and cover all parts of the sac. Sometimes assistance is given by a thread clipped to neighbouring arachnoid with a silver clip. Frequently a sheet of gutta-percha placed beneath the sac has acted as an efficient hammock to aid in moulding the acrylic, especially in relation to the optic chiasma and basal cisterns. Should one be unable to remove the stamp after polymerization is "complete," the excess can be trimmed away and no harm ensues from the retained fragment. On all occasions the optic chiasma has been screened and no visual field defects have been noted.

Premature rupture has been treated by means of a clip applied at any convenient distance from the neck of the sac (if possible) to secure haemostasis. The sac remnant, clip, and parent vessel can then be invested. This method can be adapted to treat large aneurysmal sacs. Middle cerebral aneurysmal ruptures have also been dealt with fairly easily by means of a temporary proximal ligature (thread) on the middle cerebral artery, a hammered muscle graft applied, and the whole then invested.

Conclusion

This method would appear to be safe and effective, and should be accepted as a recognized means of treating aneurysmal sacs not suitable for other methods. Personal communications indicate that this method has now been tried in different clinics throughout the world and without any apparent drawbacks (af Björkesten and Troupp, 1958).

Experimental work has established its acceptance and tolerance by the body and freedom from sepsis. A follow-up of the patients during a three-year period indicates its effectiveness. On certain occasions, especially cases of accidental rupture, it has definite advantages, and has proved of great value in difficult situations. Furthermore, experience has shown that its use has not been associated with the spasm of local arteries which can so disastrously affect the outcome of a potentially successful case after ligation.

Summary

Acrylic investment has been found satisfactory in experimental work and in a three-year follow-up of patients.

Seventeen cases with subarachnoid haemorrhage have been treated—nine due to aneurysms of the anterior communicating artery and eight affecting the middle cerebral artery.

The middle cerebral group did uniformly well. Two of the anterior communicating series died after operation from causes not directly attributable to the method.

The technique is simple and asepsis is easily achieved.

Certain advantages of the method have become apparent with experience.

It is a pleasure to record my indebtedness to my neuro-surgical preceptor, Mr. George Alexander, and to my

colleagues at the South-western Regional Neurosurgical Unit, Mr. Douglas Phillips and Mr. Allan Hulme, who encouraged me to make use of the method in their cases and for allowing me access to their notes, and to specially thank Mr. G. F. Rowbotham, of the Regional Centre of Neurological Surgery, Newcastle upon Tyne, who also referred three cases to me. I am especially grateful to Dr. R. M. Norman and Dr. R. Sandry, of the Neuropathological Laboratory, Frenchay Hospital, Bristol, for the histological studies. I also wish to acknowledge the grant made by the University of Bristol Department of Surgery and to Professor Masservy and staff of the Veterinary College, Langford, for facilities for the preliminary experimental work.

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SERUM AMYLASE ESTIMATIONS IN DIFFERENTIAL DIAGNOSIS

BY

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"The diastase content of each individual is very constant, so that deviations from this normal value are significant" (Somogyi, 1938, 1941). The simplest laboratory investigation used in differentiating acute pancreatitis from other "acute abdomens" is the serum amylase estimation. Occasional rises encountered in other abdominal emergencies (Burnet and Ness, 1955), after the administration of opiates (Wapshaw, 1953), in mumps (Wolman *et al.*, 1947), after alcohol (Carter, 1945), in renal failure and other miscellaneous conditions (Polowe, 1946), have thrown doubt on its value. This study is a critical evaluation of a rapid "side-room" serum amylase estimation in conditions which often present as a differential diagnosis of acute pancreatitis. In addition, the case histories of those conditions other than acute pancreatitis where a rise was encountered have been analysed to try to demonstrate any common factors.

For the purposes of this study serum amylase estimations were carried out on 454 patients, divided as follows: (*a*) 45 cases of pancreatitis (41 acute and 4 chronic) in which the diagnosis was made in 32 cases on clinical grounds in conjunction with a raised serum amylase, in 11 cases by laparotomy, and 2 cases at necropsy (Table II); (*b*) 337 cases of conditions recorded as the differential diagnosis of acute pancreatitis; and (*c*) 72 miscellaneous causes of acute abdominal pain.

Method.—The method used was a modification of Somogyi's iodometric technique as described by King (1946). This measures the rate of hydrolysis of a standard starch solution (75 mg./100 ml.) by the amylase at 37° C. to erythrodextrin, achrodextrin, maltose, and glucose. Sampling was carried out at 30 seconds and one minute, then at two-minute intervals, reverting to intervals of 30 seconds when the end-point (a final disappearance of any blue colour) was neared. A normal range of 60 to 200 units/100 ml. was established.

TABLE I.—*Serum Amylase Estimations in 454 Cases*

Diagnosis	Serum Amylase (Units/100 ml.)				Total No. Cases
	<200	200–355	400–640	800+	
Acute appendicitis ..	85	5	Nil	Nil	90
Exacerbation of peptic ulcer	81	6	"	"	87
Perforated viscus ..	20	12	2	1	35
Intestinal obstruction ..	29	5	Nil	Nil	34
Coronary thrombosis ..	30	Nil	"	"	30
Acute cholecystitis ..	55	5	"	1	61
Miscellaneous	67	4	"	1	72
Acute pancreatitis ..	Nil	2	12	27	41
Chronic pancreatitis ..	2	1	1	Nil	4

Precautions

(*a*) Blood for serum amylase estimation was taken in all cases prior to operation or administration of morphine derivatives.

(*b*) McGeachin (1953) stated that no deterioration in serum amylase activity occurred in serum stored at 4° C. for periods up to 72 hours. Six out of 30 consecutive serum amylases of the early cases, redetermined after refrigeration at 4° C. for periods varying from 12 to 24 hours, showed some diminution in activity. In consequence, all estimations were carried out immediately the blood samples had been taken.

(*c*) Salivary contamination of the starch substrate was prevented by incorporating cotton-wool filters in all pipettes.

(*d*) Amylase-producing organisms may be introduced into the substrate and cause deterioration. The commonest significant natural contaminants, shown by daily cultures of the substrate, were starch-splitting organisms of the *Bacillus subtilis* group. Estimations using starch solution grossly contaminated with these cultures were compared with the results using uncontaminated starch and after seven days with a freshly prepared substrate. No deterioration occurred over this period provided the solution was refrigerated when not in use. In consequence starch substrate was prepared freshly every week, stoppered, and refrigerated between estimations.

(*e*) The difficulty of recognition of the end-point in artificial light or with bile-stained serum was obviated by the use of a white tile, on to which equal volumes of the sample and iodine were placed.

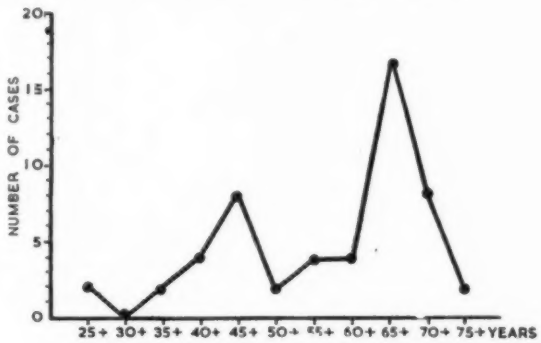
Acute Pancreatitis

The ranges of serum amylase encountered in the 41 cases of acute pancreatitis can be seen in Table I. Twenty-four were 1,100 units or above, and all determined within 24 hours of the onset of symptoms were 533 units or greater. A pre-operative diagnosis of acute pancreatitis was made only once without the aid of enzyme studies, and here laparotomy had to be resorted to for confirmation (Case 35, Table II). Four of the 15 other cases proved by laparotomy (Cases 3, 5, 19, and 57) died post-operatively, whereas only 2 of the 25 with a raised serum amlyase treated conservatively were fatal.

TABLE II.—*Serum Amylase Values in Acute and Chronic Pancreatitis*

Case No.	Sex	Age	Differential Diagnosis	Mode of Confirmation	Serum Amylase (Units/100 ml.)	Eventual Outcome	Comments
1	F	45	Acute cholecystitis	Clinical	3,200	Recovery	
2	M	68	Ac. cholecystitis and perforation	,,	1,600	,,	
3	F	40	Perforation ..	Laparotomy	650	Death	
4	M	65	Ac. cholecystitis and int. obstruction	Clinical	533	Recovery	
5	F	65	Perforation ..	Laparotomy	None	Death	
6	F	65	Int. obstruction	,,	100	Recovery	Chronic
7	F	59	Perforation and ac. cholecystitis	Clinical	3,200	,,	
8	F	46	Perforation and biliary colic	,,	3,200	,,	
9	F	66	Cor. thrombosis, perforation, and exacerbation of duodenal ulcer	,,	1,600	,,	Confirmed at laparotomy 6 months later
10	F	73	Perforation or exacerbation of duodenal ulcer	,,	533	,,	
11	F	72	Cor. thrombosis and exacerbation of duodenal ulcer	,,	1,600	,,	
12	M	60	Ac. cholecystitis and exacerbation of duodenal ulcer	,,	800	,,	Laparotomy refused
13	M	66	Perforation ..	,,	1,100	Death	P.M. refused
14	F	47	Pancreatitis ..	,,	1,600	Recovery	
15	M	44	Perforation ..	,,	3,200	,,	
16	M	67	Perforation of duodenal ulcer	Laparotomy	400	,,	
17	M	55	Pancreatitis ..	Clinical	1,600	,,	
18	M	50	Exacerbation of duodenal ulcer	,,	533	,,	Amylase 2 days after onset
19	F	78	Ac. cholecystitis	Necropsy	None	Death	
20	F	66	,, ,,	Clinical	1,600	Recovery	
21	F	69	,, ,,	Laparotomy	533	,,	Laparotomy 2/12 later confirmed
22	F	68	Ac. appendicitis	,,	None	,,	
23	F	65	Perforation ..	,,	,,	,,	
24	F	63	Perforation or cor. thrombosis	,,	,,	,,	
25	M	72	Carcinoma of stomach	Clinical	320	,,	Chronic
26	F	68	Perforation ..	Laparotomy	400	,,	Post-op. amylase
27	F	55	Biliary colic ..	Clinical	800	,,	
28	F	67	Stone in common bile duct	,,	800	,,	*X*-ray confirmation
29	M	61	Cholecystitis ..	Laparotomy	620	,,	
30	M	47	Exacerbation of duodenal ulcer	,,	640	,,	
31	M	73	Cholecystitis ..	Clinical	1,600	,,	
32	F	41	Biliary colic ..	,,	1,600	,,	
33	M	43	Cholecystitis ..	,,	1,066	Death	P.M. confirmed
34	F	65	Cor. thrombosis or cholecystitis	,,	1,600	Recovery	
35	F	46	Pancreatitis ..	,,	400	,,	Amylase 2 days after onset
36	F	47	Ac. cholecystitis	,,	3,200	,,	
37	M	25	Perforation or cor. thrombosis	Laparotomy	1,600	,,	Post-op. amylase
38	F	47	Pancreatic cyst	,,	400	,,	Chronic
39	F	46	Perforation ..	Clinical	230	,,	3 days post-op.
40	F	45	,, ..	Laparotomy	None	,,	
41	M	44	,, ..	Clinical	1,600	,,	
42	F	65	,, ..	Laparotomy	320	,,	2 days after onset
43	F	68	Carcinoma of stomach	,,	None	,,	
44	F	82	Ac. cholecystitis	Necropsy	80	Death	5 days after onset. Chronic
45	F	71	Ac. cholecystitis or ac. appendicitis	Clinical	None	Recovery	Urinary diastase 250 units
46	F	57	Hydronephrosis	Laparotomy	,,	,,	
47	M	72	Coronary thrombosis or perforation	,,	,,	,,	Urinary diastase 500 units
48	F	63	Perforation ..	,,	,,	,,	
49	F	72	Ac. cholecystitis	,,	,,	,,	
50	F	73	Biliary colic ..	Clinical	1,600	,,	
51	F	65	Ac. cholecystitis	,,	533	,,	1 day after onset
52	F	66	,, ,,	,,	1,600	,,	
53	F	68	,, ,,	Laparotomy	None	,,	Chronic
54	M	55	Pancreatitis ..	Clinical	2,400	,,	
55	F	45	Ac. exacerbation or perforation or ac. cholecystitis	,,	1,600	,,	
56	F	35	Ac. cholecystitis	,,	1,600	,,	Post-puerperal pancreatitis
57	F	70	Perforation ..	Laparotomy	1,100	Death	1 day after onset
58	F	43	Ac. cholecystitis	Clinical	400	Recovery	3 days after onset

The age range was 25 to 78 years, with an arithmetric mean of 59 years (see Chart). The ages recorded showed two well-marked frequency peaks between 40 and 45 years and again between 60 and 70 years. Forty-one cases were female and only 17 male.



Age incidence of patients with acute pancreatitis.

The serum amylase generally fell rapidly in 48 to 72 hours in those cases with an initially high level, but was still above the upper limit of normal in a moderate number of cases after seven days.

Three cases in this group are of particular interest in that they reflect on the varied aetiology of acute pancreatitis and on possible explanations of a raised serum amylase in other conditions.

Case 28.—An obese woman of 67 was admitted for routine cholecystectomy and was found at operation to have, in addition to chronic cholecystitis and cholelithiasis, numerous small pigment stones in the common bile duct. A choledochogram on the 16th day after the operation showed a filling defect suggestive of a calculus at the lower end of the common bile duct. On the 18th day she complained of severe colicky pain in the right hypochondrium, and this was accompanied by generalized guarding and tenderness. The serum amylase at this stage was 800 units/100 ml. No morphine derivatives had been given within the previous 14 days. The "T" tube drainage was replaced by a small catheter, continuous suction was applied and after a stormy convalescence she fully recovered. It is a reasonable assumption that this patient had a stone at the lower end of the common bile duct which obstructed the ampulla of Vater, causing reflux of bile along the pancreatic duct and a mild pancreatitis.

Case 30.—A man aged 47 was admitted as a case of acute exacerbation of a duodenal ulcer and treated

conservatively with apparent success; three days later, however, he had a severe recurrence of epigastric pain. This was accompanied by profuse vomiting. On examination there was rebound tenderness over the whole upper abdomen. The serum amylase was 640 units/100 ml., and laparotomy one hour later revealed an abscess on the lesser curvature of the stomach which had ruptured into the pancreas. This case well illustrates how inflammation of adjacent viscera may involve the pancreas and cause a rise in serum amylase.

Case 56.—An obese woman of 35 experienced a sudden attack of severe colicky upper abdominal pain two weeks after the birth of her child. The pain was unremittent, lasting 36 hours—that is, until analgesics gave relief. The only physical sign was epigastric tenderness. The serum amylase on admission was 1,600 units/100 ml., and all subsequent investigations, such as barium-meal and Graham's *x*-ray etc., were negative. I regard this case as an example of post-partum pancreatitis as described by Joske (1955).

Perforated Peptic Ulcer

It is significant that 10 out of the 14 cases (Table II) of acute pancreatitis subjected to laparotomy had a differential diagnosis of perforated peptic ulcer, and *pari passu* with this the highest percentage of cases with a raised serum amylase (15 out of 35 cases) occurred in this disorder. However, in only three cases were the figures above 533 units/100 ml., and in one of these, already described (Case 30), the ulcer had given rise to a perigastric abscess which subsequently ruptured into the pancreas. The highest value recorded was 1,600 units/100 ml. in a middle-aged man who had an anterior perforation of the first part of the duodenum. The second, of 640 units/100 ml., occurred in a similar case of perforation of the duodenum, but was accompanied by pre-gangrenous changes in the ileum, and this patient subsequently died. In neither case was the pancreas adequately examined, and there was no obvious explanation for the rise. The 12 remaining cases had values ranging between 200 and 400 units/100 ml., generally well below those encountered in acute pancreatitis of similar duration. Probstein *et al.* (1949) believe that serum amylase could be of value in differentiating an anterior from a posterior duodenal perforation. Table III, an analysis of cases with amylase values of 200 units/100 ml. and over, fails to confirm this.

TABLE III.—*Serum Amylase Values in Cases of Perforated Peptic Ulcer in Relation to Site and Duration of Perforation*

Serum amylase	200	200	260	266	320	320	375	640	640	1,600
Site	Ant	Post	Ant	Post	Ant	Ant	Ant	Post	Ant	Ant
Duration in hours	3	4	72	5	2½	8	5	2	48	3½

Intestinal Obstruction

In this group only 5 out of 34 estimations were above 200 units/100 ml., and the highest recorded was 355 units/100 ml. Two of these are of interest in that their histories and findings suggest a possible explanation of this rise.

Case A.—A man aged 72 was admitted with abdominal distension and vomiting. He was hypertensive, and on examination had minimal tenderness and guarding in the epigastrium. His symptoms subsided on conservative treatment, but a subsequent barium enema showed marked distension of the small bowel and fluid levels suggesting a partial obstruction. A barium meal at a later date showed a fullness in the region of the pancreas with displacement of the duodenal loop. The serum amylase on two successive days was 320 units/100 ml. As the radiologist suggested, this patient probably had a pancreatic cyst, a condition sometimes associated with a high serum amylase.

Case B.—A woman aged 54 complained of severe generalized colicky abdominal pain of sudden onset, associated with vomiting and diarrhoea of 24 hours' duration. On examination she was shocked and hypotensive, and had generalized abdominal guarding, rigidity, and absent bowel sounds. The serum amylase was 320 units/100 ml., and a diagnosis of a perforated viscus was made. Laparotomy revealed gangrene of the whole of the small intestine, suggesting a mesenteric thrombosis. A subsequent necropsy confirmed this. The thrombus was occluding the whole of the lumen of the superior mesenteric artery for a distance of 3 cm. from its origin.

It is reasonable to assume the rise in serum amylase in Case B resulted from pancreatic ischaemia secondary to obstruction of the inferior pancreatico-duodenal artery. By contrast, a fatal case of a mesenteric embolus obstructing the first major branch of the superior mesenteric artery had a normal serum amylase. This differed only in that the patient was not hypotensive when the serum amylase was determined, the clinical presentation of these two cases being identical.

Coronary Thrombosis

One of the 12 cases of acute pancreatitis (Case 9) in which E.C.G. recordings were made showed changes suggestive of a posterior infarction. Burn (1951) remarked on the close association of focal pancreatitis and coronary thrombosis at necropsy—later confirmed by other workers. In two of his cases the serum amylase had been markedly raised before death. He failed, however, to indicate whether morphine derivatives had been administered, and by contrast none of the 34 cases of myocardial infarction studied in this series had a serum amylase greater than 200 units/100 ml.

One case deliberately investigated at intervals after ⅙ gr. (10 mg.) of morphine had been given intramuscularly gave the following results (the serum amylase figure immediately prior to injection being 160 units/100 ml.

Time after Injection	1½ hours	3 hours	12 hours	18 hours
Serum amylase	353 units	800 units	640 units	320 units

These values correspond to those observed in normal individuals after opiates by Wapshaw (1953), the rise still being maintained after 18 hours.

Acute Cholecystitis

Table II shows that 21 out of 53 cases of acute pancreatitis had a provisional diagnosis of acute cholecystitis. Only 6 of the 61 cases with this disease showed a rise of serum amylase, but none were within the range commonly seen in acute pancreatitis. The greatest activity was 800 units/100 ml., recorded in only one case. All five cases were obese and hypertensive, but as both these were common findings in this group they must be accepted as of no significance.

Acute Appendicitis

Five cases of 90 investigated in this group had a raised serum amylase. The elevations were slight, the maximum being 266 units/100 ml. This was recorded in two fatal cases, one of which was found at necropsy to have polycystic kidneys. It is conceivable that inadequate urinary amylase excretion, concomitant with the hypotension existing in both these cases when the determinations were made, could account for the slight

rises. There was no constant relation between the severity of the inflammation and the serum amylase level.

Exacerbation of a Peptic Ulcer

Only 6 out of the 87 cases of exacerbation of peptic ulcer investigated had figures greater than 200 units/100 ml., and the highest recorded (one case) was 355 units/100 ml. No explanation for these slight elevations could be drawn from detailed analysis of these case histories.

Miscellaneous Group

Barratt-Boyes (1957) describes six cases of ruptured aortic aneurysm, all with a normal serum amylase, in which the first differential diagnosis was acute pancreatitis.

This group included two cases of saccular arteriosclerotic abdominal aneurysms of identical size and distribution—that is, extending from the renal arteries to the bifurcation of the aorta. In the first the serum amylase, recorded two days after retroperitoneal rupture when the patient was shocked and hypotensive, was 800 units/100 ml. The second, determined when the preliminary leak was occurring (shown at laparotomy) and the patient hypertensive, was 230 units/100 ml. Here, compression or obliteration of the inferior pancreatico-duodenal artery, plus diminished urinary amylase excretion in the first case (secondary to the hypotension), were probably responsible for the rise in serum amylase.

One of the two cases of malignant hypertension in this group, with a grade IV retinopathy in a terminal phase, had a serum amylase of 320 units/100 ml., whereas the second, less severely affected, had a normal value. The rise in the first case may have resulted from pancreatic arteriolar damage or have been secondary to poor urinary amylase excretion.

Levels of 355 units/100 ml. in a proved case of sarcoidosis and 320 units/100 ml. in a case of pyrexia of unknown origin with associated meningism were encountered in this group. The former, sustained on two successive days, might conceivably have been due to pancreatic involvement in the sarcoid process.

The second patient had some injection of the fauces, cervical lymphadenopathy, and raised E.S.R., but all other laboratory investigations were negative. Unfortunately, serological investigations to exclude a mumps encephalitis were neglected.

Ten cases of renal colic and 10 with ruptured ovarian cysts included in this section had normal amylase values.

Discussion

This simple estimation, shown by Burnett and Ness (1955) to be suitable for ward side-room use, is as reliable as more detailed methods provided the precautions outlined in its description are observed and the investigator is solely concerned with a rise in amylase activity. Table I demonstrates the consistently high values which occur in acute pancreatitis, as compared with those encountered in conditions which are often its differential diagnosis. Its value in differentiating coronary thrombosis, acute cholecystitis, exacerbation of a peptic ulcer, and acute appendicitis from acute pancreatitis is well substantiated by these findings. The serum amylase in all cases of acute pancreatitis, determined within 24 hours of the onset of symptoms, was 533 units/100 ml., or greater, but in five cases investigated after long periods values in the range 200 to 400 units/100 ml. were encountered.

Interpretation of results must therefore not only take into consideration the previous administration of morphine derivatives and any co-existent parotitis, but also whether the symptoms are subsiding and their duration prior to the estimation.

Critical levels quoted by previous authors are to be deplored, as occasionally very high values are encountered in other conditions, particularly in cases of perforated peptic ulcers where there is no demonstrable macroscopic pancreatic disease. It cannot be too strongly stressed that the serum amylase estimation is never pathognomonic and should never be allowed to outweigh the clinical assessment. The possible sources of serum amylase are pancreas, salivary glands, serozymogenic glands of the small intestine, and amylase-producing intestine organisms.

The rise encountered in conditions other than acute pancreatitis is relatively easy to explain in some cases; for example, Case 28—obstruction of the ampulla of Vater with a small stone and reflux of bile up the pancreatic duct; while in Case 30 actual local destruction and inflammation of pancreatic tissue by a perigastric abscess was demonstrated at laparotomy. Similarly, partial or complete obstruction of pancreatic arteries in vascular catastrophes such as ruptured aortic aneurysms seems a logical explanation of the raised serum amylase.

The slight rise encountered in other intra-abdominal conditions, however, is more difficult to account for, but presents an interesting problem. Burnett and Ness (1955) postulate that the raised values encountered in perforations are related to duration and degree of peritoneal contamination, with consequent absorption of the normal pancreatic enzymes. It was not possible to confirm this (Table III). An estimation of these factors is fraught with difficulty, as the duration is affected by the presence or absence of an omental seal and it is impossible to measure the degree of peritoneal contamination with any accuracy. Dilatation, inflammation, or decreased viability of the intestinal wall, such as occurs in intestinal obstruction or an acute appendicitis, might result in increased absorption of intestinal amylase from glands or occasionally from the amylase-producing organisms resident there (Burnett and Ness, 1955).

Normal urinary amylase concentration is two to six times the normal serum amylase (Polowe, 1946), hence any impairment of this normal excretion as the result of frank renal disease or secondary to hypotension might lead to a rise in the serum amylase level. This effect of renal disease is well illustrated by a case which at necropsy had post-operative strictures of both ureters, bilateral pyonephrosis, and a perinephric abscess. The N.P.N. was 160 mg./100 ml., serum amylase 400 units/100 ml., and a random urine amylase less than 5 units, before death. Hypotension (a systolic pressure below 80 and a diastolic less than 40) occurred over varying periods in 12 cases of this series, and 10 of these had values ranging from 200 to 400 units/100 ml.

Antiperistalsis with reflux of intestinal secretions into the pancreatic duct, or associated neuromuscular imbalance leading to a spasm of the sphincter of Oddi, can result in activation of trypsinogen and thus account for the occasional raised amylase in intestinal

obstruction. Both these conditions may occur as a result of excessive vomiting. In the present series no significant association could be demonstrated between excessive vomiting and a raised serum amylase. For example, out of 11 cases having severe protracted vomiting, seven normal values and the remaining four, with raised levels, were also hypotensive. Dehydration, enhanced by vomiting and consequent vagal stimulation, could give rise to inspissation of the pancreatic secretion and occlusion of the smaller pancreatic ducts. This, in the presence of an actively secreting pancreas (after a meal), could lead to rupture of acini and enzyme absorption into the blood stream. Twelve cases in this series were grossly dehydrated, but only four had a raised serum amylase, and of these two were in addition hypotensive.

Adrenalectomy and hypophysectomy in dogs are both followed by a transient rise in serum amylase (Cope *et al.*, 1938), suggesting that these glands are intimately connected to the exocrine pancreas. Does the exocrine pancreas respond to stress or could adrenal cortical depression in some cases account for a rise in the serum amylase? There was no constant relation in this series between cases clinically described as "shocked" and the serum amylase level. Six cases of hormone-dependent breast carcinomatosis subjected to hypophysectomy or combined with adrenalectomy had serum amylase estimations determined pre- and post-operatively. None of these cases showed any significant post-operative rise, the highest recorded figure being 230 units/100 ml.

From these analyses of the case histories it is probable that many factors may be operative, either singly or together, in causing a rise in the serum amylase in an individual case. These variables must obviously be taken into consideration in the evaluation of any raised serum amylase.

Summary

A simple method of serum amylase estimation is critically reviewed and precautions essential in its use are described.

Serum amylase values in 41 cases of acute pancreatitis, 320 cases of conditions clinically confused with acute pancreatitis, and 89 miscellaneous conditions clearly substantiate the value of the serum amylase estimation in the differential diagnosis of acute abdominal pain.

Theories of the mode of production of a raised amylase in conditions other than acute pancreatitis are reviewed and, where possible, correlated with the clinical findings.

I appreciate the co-operation shown to me by the surgical staff at Walton Hospital, Liverpool. I thank Dr. H. E. Vickers and Miss P. Kennedy for their encouragement and helpful criticism during the preparation of this paper.

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"PHISOHEX" AND SAFER SURGERY

BY

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Widespread concern about cross-infection in surgical wards has led to a more precise revaluation of many aseptic techniques, but some long-established and comforting rituals tend to escape this scrutiny.

The need for an improved surgical scrub technique became apparent during an investigation into sepsis rates in two surgical units of this hospital group. Using a standard classification of sepsis (Howe, 1957), it was shown that of 600 clean operations performed over a period of several months 10% developed major sepsis. Each unit had 33 beds for male and 33 for female pa'ients, and the total of 132 beds was increased if surgical emergencies demanded. A wide variety of surgery was performed, including many emergency cases, but only those where it was believed that primary healing should occur were included in the study.

As part of the study an investigation of contact cross-infection in operating theatres was made. The incidence of glove puncture was found to be 30% in over 1,000 gloves, and experiments confirmed that organisms rapidly passed from the operator's skin to the glove exterior provided the glove was punctured and wet (Webster, 1958). Contamination therefore seemed to be possible in virtually every operation where the minimum team was three and where six gloves were either on or near the operating site. There was great variation in the time taken for a surgical scrub, the maximum being eight minutes using brush, soap, and running water. Surgeons apparently chose cleaning agents haphazardly or by individual preference from three different cake soaps, all available in the basins. These were common yellow or green soap and a hexachlorophane soap.

As the most troublesome of hospital pathogens, *Staphylococcus aureus*, is resistant to ordinary cake soap (Bayliss, 1936), it seemed possible that the adoption of a standard surgical scrub technique capable of achieving and maintaining the superficial bacterial cleanliness of the hands throughout the operation would minimize one possible source of the contamination of clean wounds. Several chemical products said to be capable of a sustained superficial sterilizing effect upon the skin are now available; of these the most desirable would appear to be a true soap substitute which simultaneously solves the problem of soap alkali allergy. An experiment was accordingly made with a soapless detergent cream incorporating 3% hexachlorophane, with a *p*H of 5.5, the same as skin. The soapless detergent, "phisoderm" is a water-miscible anionic detergent cream. It contains a sulphonated ether, wool fat, cholesterols, and petrolatum, and is a surface tension reducent 40% more powerful than soap. The remarkable effectiveness of

hexachlorophane as a skin disinfectant has already been described (Seastone, 1947). The detergent–disinfectant combination has been favourably compared with other detergents and antibacterial agents (Hufnagel *et al.*, 1948), and is marketed under the trade name of "phisohex." It was made available to us through the courtesy of Bayer Products Limited.

The Experiment

The surgical teams involved came from the two units where the infection rate had been assessed.

Methods of assessing the contamination of the hands of an operating team at the conclusion of an operation are naturally difficult, and ultimately the "streak plate" technique was adopted. The operator removed one glove, shook any excess glove powder off his fingers, and then pressed the pads of four finger-tips on a plain agar plate. He then drew his finger-tips firmly over the surface of the agar, thus making four parallel streaks (Fig. 1). This was repeated with the second hand. The plates were then incubated for 24 hours and the numbers of colonies were counted and recorded. Growths were rarely so profuse that no count could be made, but when it occurred the result was recorded as "confluent." As expected, the amount of contamination of the hands of the operating team at the conclusion of an operation was very heavy (see Table, Phase 1).

All soap was then withdrawn from the theatres involved in the test, and phisohex dispensers—either foot-operated or small squeeze-bottles—were substituted. The subjects then scrubbed for a period of three minutes, first using a brush with phisohex and water to clean the finger-nails and then phisohex and water alone to clean the hands and forearms. A further series of "streak plates" was collected, and again the colony counts were assessed (see Table, Phase 2). The agar plates for this part of the experiment incorporated 1% "tween 80," which inactivates phisohex.

Finally, after phisohex had been used for four weeks it was withdrawn and soap was reintroduced to the operating theatres. Streak-plate counts were again done, but this third test period began one month after the withdrawal of phisohex. This interval was arranged so

FIG. 1.—Showing colonies of organisms found with the streak-plate method.

Post-operative "Plate Streak" Counts from Two Operating Teams

	Theatre 1								Theatre 2							
	Surgeon		Registrar		House-surgeon		Nurse		Surgeon		Registrar		House-surgeon		Nurse	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Phase 1 Soap scrub	108 11	115 500 180 C 12 220 120 200 C 400 100	51 C 8 3 550	47 26 7 61 139 73 79 20 C 8	10 C 145 C 60 0 69 C 127 157 56	294 1,000 156 23 134 31 64	27 250 C C 144 89 18 250 138 7	1,000 400 41 C 38 800 500	176 200 C 120	9 5 190 511 13 64	Absent	56 26 60 59 0	7 2 38 106	276 250 100 93 100 C	0 0 2 10 150 2	14 5 63
Phase 2 Phisohex scrub	Absent	7 6 1 7 3 7 9 1 5 48 2 0	0 8 0 54T 0 0	Absent	0 2 0 3 0 0	0 0 0 0 0 1 0 0 1 5 0	0 0 0 0	18 0 0 0 0	0 500T 6 5 0 0	0 0 0 7 0	71 0 0 0 5 0	2 0 1 0 1 0 0 0 0 0 0 8	1 1 1 0 0 1 0 0 0 0 0 0 1 2	1 1 0 0 0 0	0 49 0 0 0 0 0 0 10 1 2 0 0 0 0	0 0 0 0 16 0 0 0
Phase 3 Return to soap scrub	6 1 49 45 5 119 8	C 533 235 216 600	Absent	Absent	5 10 232 4 90 75	141 526 190 324 363 194 318	14 14 154 107 40 321 295 C 83 157 50 162 174	40 29 84	116 950 230 145 600 195	25 12 127 442 18 118 145 130 48 89	Absent	420 123 41 22 95 140	2 5 55 0 9 40 85 97	9 92 190 129 162 85	5 4 57 18 70 110	10 30 63 30 90 120

A and B denote separate individuals in each surgical team. C="Confluent"—that is, growths so profuse that count could not be made. T=Counts obtained when gloves were torn.

as to allow the re-establishment of skin flora. Sampling on this occasion was carried out with equal numbers of plain agar plates and plates incorporating 1% tween 80 (see Table, Phase 3).

Glove-puncture rates were not noted, but the Table contains the letter T opposite counts obtained at a time when gloves were noticeably torn.

Bacteriology: Control of Experiment

Before the reduced counts after phisohex scrubs could be taken as significant it was considered imperative to assess the ability of tween 80 to inactivate any phisohex transferred from the operator's finger-tips to culture media during sampling.

Earlier work (Lawrence and Erlandson, 1953) shows tween 80 to be much more effective than either fresh human serum or its fractions as an inactivator of hexachlorophane. Phisohex, however, uses the soapless detergent "phisoderm," itself mildly bacteriostatic, as a vehicle for hexachlorophane. Consequently an assessment of the inactivating power of tween 80 in this experiment had to include its action against both phisohex and its two principal constituents. This was done as follows:

1. Plates showing negative cultures after streaking with phisohex-scrubbed fingers were immediately re-streaked with unwashed fingers or inoculated with diluted broth cultures of staphylococci. Reincubation of these plates showed no evidence of growth inhibition.

2. During the latter part of the trial of phisohex, fresh human serum agar plates were used for sampling in parallel with tween 80 agar plates. A comparison of these plates showed that growths, if any, were always greater on tween 80 agar.

3. Four rabbits were used to provide comparable areas of shaved and artificially contaminated skin. Bacteriological sampling of these sites following a phisohex scrub and rinsing with distilled water revealed growth of the test staphylococcus on tween 80 agar but not on plain nutrient agar.

4. Ten 1% tween 80 agar plates and 10 nutrient agar plates were flooded with 10 dilutions of phisohex, varying from 1:5 to 1:1,000, and an exactly similar set of plates was flooded with dilutions of phisoderm varying from 1:5 to 1:90. After drying, all plates, plus two control plates, one of tween 80 agar and another of nutrient agar, were inoculated with a known number of pyogenic staphylococci. After incubation, nutrient agar plates showed complete inhibition of all growth by phisohex, up to and including a dilution of 1:200 and by phisoderm only to a dilution of 1:5. All tween 80 agars showed uninhibited growth in every dilution of phisohex or phisoderm.

Bacteriology of Trial

Streak plates were incubated at 37° C. for 24 hours. Colony counts were then recorded and the plates stored on the laboratory bench for a further 48 hours. They were then examined for the presence of *Staph. pyogenes*, which was confirmed only after the demonstration of coagulase production by the slide method, or, if this was inconclusive, by the clotting of plasma in a test-tube.

Results

As seen in the Table, the bacterial colony counts fell rapidly and significantly when phisohex was used. They disappeared altogether in the case of one individual, while the majority of the other participants had approximately twice as many sterile culture plates as they did contaminated plates. Only one individual showed successive small counts while using phisohex, and this was the person with the highest total counts while using soap. When phisohex was used the highest counts generally appeared either at the beginning of a week after a week-end's rest from surgery, or if gloves were torn and fingers blood-stained during dirty operations.

Growths consisted almost entirely of saprophytic skin cocci, but *Staph. aureus* was also present in very small numbers in five of the samples following soap scrubs. In these samples this pathogen appeared as an occasional colony in otherwise heavy growths.

Fig. 2 summarizes the comparable results in the Table by showing the average colony counts obtained from individual members of the surgical team who were

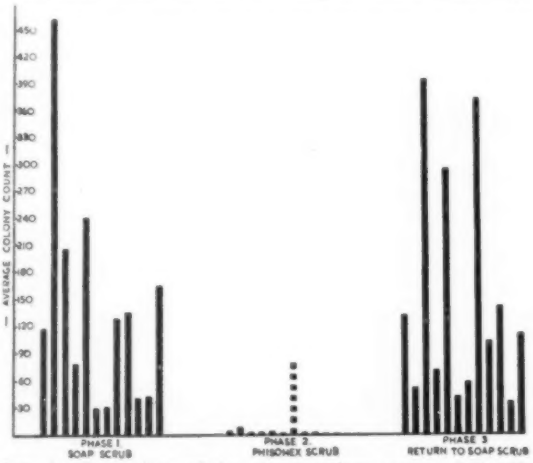

FIG. 2.—Comparison of the average colony counts of the 12 participants present throughout the experiment.

present for all three phases of the experiment. A standard value for confluent growth was not included, but this increases the significance of the comparison. The broken line in the centre of the histogram, although representing a percentage count, is largely due to a single count of 500 following a large glove tear during a dirty abdominal operation. In this culture coliforms predominated.

Discussion

With the increasing menace of high cross-infection rates, drug-resistant bacteria, and poor hospital hygiene, reappraisal of surgical scrub techniques as practised in this country seems overdue. In U.S.A. similar methods to those described in this small experiment have been in use for several years. While it is accepted that this is only one facet of a complex problem, we feel that surgical technique must be as suspect as other potential causes of hospital infection.

The results of this experiment indicate that the surgeon's confidence in his present scrub technique is unjustified. At the end of a surgical procedure, when contact with the wound is at its most intimate, the hands of the team are heavily contaminated, and, in the presence of glove puncture, which is to some extent unavoidable, passage of hand organisms through the puncture to the wound is likely. If these organisms include high-grade pathogens, as can be expected from time to time, serious infection may follow.

The preliminary results, which we have recorded, seem to us to justify the use of a soapless detergent

agent which includes an antiseptic—in this case hexachlorophane—but such a substance, as well as being effectively antibacterial, must also be non-irritant. With phisohex the problem of allergy to soap alkali does not arise. In this trial it was found soothing to the skin, caused no reactions, and was preferred by the majority of participants. On the other hand, we have evidence of hexachlorophane soap allergy in one surgeon in this hospital, and, furthermore, hexachlorophane soap is less satisfactory because of the difficulty of transferring water-insoluble hexachlorophane from soap to skin. This may be one reason why the sporadic use of hexachlorophane soaps during periods 1 and 3 of this experiment showed little or no tendency to diminish the counts. The inclusion of the water-repellent lanolin in phisohex promotes the transfer of hexachlorophane to the skin.

The scrub time of only three minutes with phisohex brought some criticisms from the surgical staff, but the bacteriological results show it to be far more effective than soap in the circumstances of this trial. The amount of suds produced was a little less than with soap, and this again caused some criticism.

It is claimed by the manufacturers that the effect of phisohex is a cumulative one. It did seem that the bacterial counts at the beginning of a week were somewhat higher than at the end, but the counts generally were so low that the differences here were not significant. Although a powerful disinfectant, hexachlorophane does not degerm skin quickly, as does 70% alcohol (Price, 1951). Consequently the bactericidal effect of phisohex can be attributed to the efficient deposition of hexachlorophane as a semi-permanent film on the skin of frequent users.

Its use might therefore be justified in the pre-operative preparation of patients undergoing elective surgery, such as, for example, certain types of orthopaedic procedure. In this instance the patient would wash frequently with the agent for two or three days before operation.

Powerful inactivation of phisohex by tween 80 agar was demonstrated during tests on the control of the bacteriological investigation. Therefore it is highly improbable that the extremely low or negative counts obtained during the trial of phisohex were due to the transfer of small amounts of this substance to the culture plates during sampling. This supports the theory that phisohex, used frequently, is cumulatively bactericidal to skin flora. Furthermore, if the deeper layers of saprophytic skin flora are dependent on environmental bacterial replenishment, then the constant presence of the phisohex film on the skin of habitual users may eventually diminish those reservoirs of bacteria which are beyond the reach of the scrubbing-brush.

The experiment was too short to gauge the effect on wound sepsis in the surgical units involved, but sepsis rates certainly did not rise during the period.

Summary

An effective and convenient technique of surgical scrubbing is described.

The assessment of the efficiency of the scrub agent—phisohex—was determined by the fall in the number of bacterial colonies as estimated by a "streak plate" technique.

The result, which was controlled by the use of culture media inhibitory to phisohex, showed that the new method produced a highly significant fall in the number of colonies of skin organisms grown from the finger-pads of the surgical team at the end of operations.

The advantages and disadvantages of phisohex and hexachlorophane soap in the surgical scrub are discussed.

We thank Professor A. Macdonald, professor of bacteriology, for helpful criticism and advice, and the surgeons and theatre staff of Aberdeen Royal Infirmary for their co-operation.

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CORRECTION OF UNIOCULAR APHAKIA BY MEANS OF ALL-ACRYLIC ANTERIOR-CHAMBER IMPLANTS

REVIEW OF 100 CASES

BY

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In 1951 Harold Ridley described his method for overcoming the visual defect in cases of aphakia by means of an acrylic lens inserted behind the iris and in front of an intact posterior lens capsule. He was thus the pioneer of intraocular implant surgery. By 1953, however, it was evident that this technique had its limitations. The artificial lens had to be inserted at the same time as an extracapsular extraction was performed, so that there was no means of checking the aphakic correction before the implant was inserted, and the patients in whom the posterior capsule had been divided or had been removed were not eligible. Perceiving the possibilities of this technique, and in an attempt to avoid some of its disadvantages, certain workers, such as Strampelli (1954), in Italy, Barraquer Moner (1954), in Spain, and Schreck (1955), in Germany, evolved an implant placed in front of the iris and behind the cornea, with feet wedged in the anterior chamber angles and carrying a central optical portion, the correction of which could be modified to suit the requirements of the individual case (Fig. 1). This type if implant can, and indeed should, be inserted after the eye has made a satisfactory recovery from cataract surgery, thus reducing the surgical trauma inflicted upon the eye at each session.

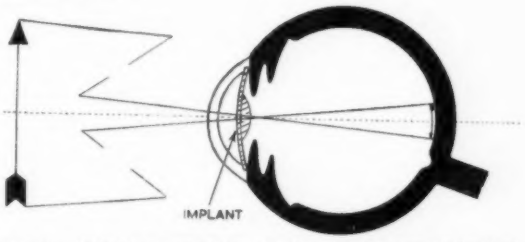

FIG. 1.—Aphakia corrected by anterior-chamber acrylic implant.

Cases of uniocular cataract or aphakia are common. While some patients accept their disability in a phlegmatic fashion, apparently satisfied to have one good eye, others suffer considerably from their threefold disability. Their unaided vision is usually less than 3/60, and, of course, they cannot enjoy the benefits conferred by binocular vision; many of them are confused and worried by their inability to use their two eyes together and develop psychological changes for the worse, this being especially noticeable in children and young adults.

Attempts to use a normal eye with an aphakic one by means of spectacles usually fail because of aniseikonia amounting to about 30% in most cases. A contact lens in the aphakic eye will reduce this disparity in image size to about 10%, but, even so, many patients cannot tolerate even this amount of aniseikonia. An anterior-chamber implant will reduce this figure still further to about 3%, which can be tolerated by the patient.

The type of implant which is used is clearly of the first importance. A one-piece implant, made of an inert material and of exactly the right length for the particular case, is the ideal. A modified Strampelli type implant has been used throughout (Fig. 2). These implants have an inner radius of curvature of 14 mm., which provides for a clearance between the central part of the posterior corneal surface and the anterior surface of the implant of between 1.5 and 2 mm. Therefore, if the implant has been correctly inserted it is nowhere in contact with the corneal endothelium.

The manufacturers (Rayner Ltd., 160, New Bond Street, London, W.1) supply the implants in 0.5-mm. sizes, from 10.5 to 14 mm., from which the surgeon can choose an implant of exactly the right length at the time of operation. The unused implants are then returned to the manufacturers. This may seem an elaborate method of obtaining a correct fit, but there appears to be no satisfactory alternative. The implants are made of fully polymerized methyl methacrylate, usually known as acrylic.

The first 30 implants were sterilized in cetrimide, which was not entirely satisfactory, for some of the sterilizing agent was adsorbed by the methyl methacrylate and, leaking out subsequently into the eye, produced some reaction. This problem seems to have been answered by Frederick Ridley (1957), who evolved a simple and economic method of sterilizing these implants with caustic soda. This method has been used in the subsequent 70 cases with consequently less post-operative reaction than with the earlier cases.

Detailed accounts of the pre-operative and post-operative management of these cases and of the surgical technique involved have already been given (Choyce, 1958, 1959).

Attention to the following points is essential: (*a*) the eye must have made a complete recovery from antecedent cataract surgery and any complications arising therefrom; (*b*) the implant must be a tight fit and must not move about the anterior chamber; and (*c*) some form of superior iridectomy is desirable.

100 cases of uniocular aphakia have been treated with anterior-chamber implants at the Southend General Hospital. Most of these patients were unsuitable for treatment with contact lenses because they were too young or too old, or because they had been given trial fittings and had been found to be liable to diplopia, or because they had used contact lenses for a year or so and given them up as they could not tolerate them.

The following Table analyses the causes of the cataract or aphakia in these cases.

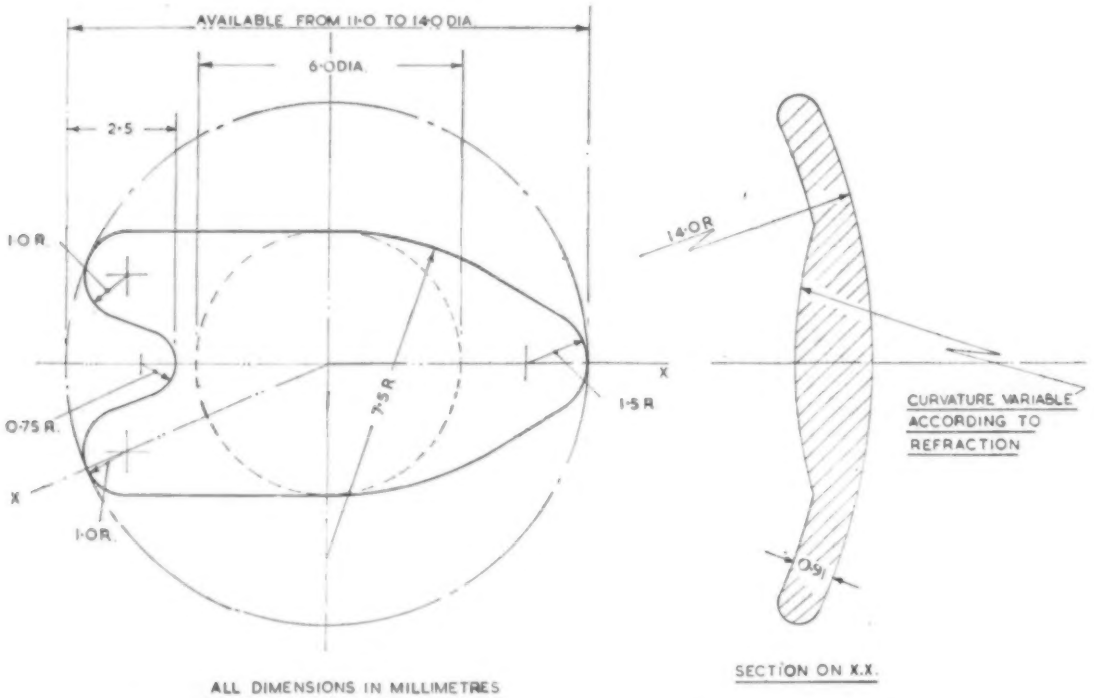

Fig. 2.—Strampelli implant for the anterior chamber. Modified by Choyce. (Diagram by Rayner Ltd.).

Causes of Cataract or Aphakia in 100 Cases

Traumatic aphakia	10 within 2 years of injury 22 within 2-56 years after injury (Implants inserted from 3 months to 56 years after injury)	32
Senile cataract, 50+ age group		40
Heterochromic cyclitis with cataract		10
"Senile" cataract, 20-50 age group		9
Unioocular congenital cataract, 2-4 age group		5
Complicated cataract from iritis with secondary glaucoma		4

Visual Acuity

By comparing the post-implant visual acuity with the pre-implant acuity obtained by the use of an aphakic correction in a spectacle frame, it is noted that in 90% of the patients the visual acuity is as good as or better than that which had been expected. The 10% of disappointments were due to the following causes:

Iritis leading to secondary glaucoma and necessitating removal of the implant	3
Endothelial corneal dystrophy (including two of the three above)	4
Cause uncertain, ? macular oedema	5
Sympathetic ophthalmia	0
Eyes enucleated	0

Only one case in the last 50 has been a disappointment, which suggests that as experience increases so should the incidence of complications lessen. Intraocular surgery is always dangerous, often difficult, and frequently disappointing, and when viewed against this background it is felt that the above list of complications is not serious.

One additional patient (aged 74) committed suicide for reasons unconnected with his eye operation six weeks after insertion of the implant. His case is not included in this series. The eye containing the implant has been examined in detail by Professor Norman Ashton, of the Institute of Ophthalmology, and a full report is in the press (Ashton and Choyce, 1959). This examination disclosed that the iris root was distorted and atrophic, and the anterior attachment of the ciliary muscle appeared attenuated and weakened so that posterior dislocation of the foot of the implant becomes a theoretical possibility. Clearly, this stretching and atrophy of the structures of the angle might be lessened if the thickness of the haptic portion of the implant could be reduced, and instructions were therefore given to the manufacturers of these implants to reduce the thickness from 0.91 to 0.50 mm.

The manufacturers have decided to call this modification the "Choyce anterior chamber implant" to distinguish it from the thicker Strampelli implant. I have now inserted several of these thinner implants and am satisfied that the technique of insertion becomes even simpler; I am continuing to use them.

Binocular Vision

Binocular vision was restored in 75% of the cases operated upon; in the remaining 25% alternating suppression had set in, usually associated with manifest squints, either horizontal or vertical or both. Where the deviation was so marked as to be noticeable, it was corrected by means of cosmetic muscle surgery. Convergence deficiency caused some difficulty in six cases; this yielded to orthoptic exercises. Diplopia could occasionally be elicited in some of these patients, but none of them complain of diplopia.

Psychological Results

Striking improvement in the morale and psychological well-being of these patients has been observed, especially in the group of young adults with traumatic cataract or traumatic aphakia. This point is best brought out by some typical case histories.

Case 1

A 20-year-old man, a Royal Marine commando, received a perforating wound of the right eye during exercises. He was invalided out of the Service and given a small pension for the loss of use of this eye. He was very much an open-air type, and he had set his heart on a career of this sort. He became very depressed, would not see any of his old friends, and made no attempt to get fresh employment. His family were very worried about him, and finally his twin brother took the initiative in sending him to me. He had a healed scar just below the centre of the right cornea to which a considerable strand of lens capsule was adherent. At the first operation this anterior synechia was divided, the strand of capsule removed, and a peripheral iridectomy performed. At the second operation, two months later, a 13.5-mm. anterior-chamber implant was inserted, with the result that he can now see 6/9 unaided and 6/4 with a small minus cylinder. He has full binocular vision and his mental state has improved out of all recognition. He is looking forward to a career in one of the overseas Colonial Police Forces.

Case 2

At the age of 14 a boy received a severe contusion injury to the right eye caused by an air-gun pellet. He was in hospital for many weeks and the history suggests that he had a large hyphaema with a secondary rise in intraocular tension. The sight of this eye was reduced to perception of light, and a divergent squint developed. At the age of 35 he married a woman somewhat older than himself, and although they were very fond of each other the sexual side of their married life was a disappointment to both because of the husband's diminished potency. His wife felt that this was due to his brooding over his eye and because, ever since the injury, he had had to put up with a great deal of unkind teasing, first from his schoolmates, and later on during his Army career and at work. She took the initiative in arranging for her husband to consult me. He was 38 when I first saw him. Owing to the period of secondary glaucoma following the original injury, the optic disk was deeply cupped and atrophic, and the field was small and the corrected vision was only 6/36. The intraocular tension was within normal limits. However, they were so anxious that everything possible should be done that I agreed to try implant surgery. A peripheral iridectomy was performed and a 12.5-mm. anterior-chamber implant inserted. At a later operation the divergent squint was reduced to about −5 degrees by muscle surgery. He was then able to see the expected 6/36 with this eye, and again the psychological benefit has been considerable. He has got himself a better job than he had had previously, and I understand that the physical side of their marriage is now satisfactory to both parties. This case shows that considerable psychological improvement can be expected even when the amount of vision which can be restored is limited by ocular damage in addition to the aphakia.

Case 3

After a blow from a piece of wood a woman developed a cataract in her left eye. This was extracted intracapsularly at the age of 60. She was a rather nervous patient and never succeeded in overcoming the visual confusion between her normal and her aphakic eyes. She tried numerous pairs of glasses, some designed to give her the use of the aphakic eye while occluding the good one, and vice versa. After some years of this she made an attempt to commit suicide by putting her head in the gas oven. Her daughter turned off the taps just in time, and she was subsequently admitted to a mental hospital as a certified patient with a diagnosis of acute depression. When I saw her first at the mental hospital she explained that if only her two eyes could be made to work together once more she would be much better in herself and would not make any further attempts on her life. Her self-diagnosis

was supported by psychiatric opinion, and she was given an anterior-chamber implant. The visual result was good, with an acuity of 6/6 and full binocular vision. Shortly after the operation she was released from the mental hospital and is apparently leading a normal domestic life.

Case 4

A Polish boy arrived in the United Kingdom in 1939 as a 1-year-old refugee. At the age of 12 he was hit in the right eye by a piece of wood, which produced traumatic aphakia. He developed a well-marked divergent squint, which was later considerably reduced by appropriate surgery. He became very depressed about his near-uniocular condition, and could not settle down in this country. He therefore applied to emigrate to Canada. In the meantime, at the age of 20, he obtained my opinion on the possibility of restoring useful sight to this eye with an anterior-chamber implant. I thought that this was possible, but at that moment he was told that he had been accepted by the Canadian Emigration Authorities and could leave in two months' time. I told him that it would not be possible to do this operation and see him through the convalescent period within this time, and that he had to choose between staying in this country for a year or so and having this operation done, or forgetting about it and emigrating to Canada. He decided that his eye was more important than emigration, and implant surgery was carried out. He now sees 6/6 and is very pleased. He has got a better job in this country, and is no longer so keen on emigrating.

Case 5

In 1944 two nurses were listening to the 9 o'clock news in the sitting-room of the nurses' home attached to a south coast hospital when one of the last shells fired by the Germans across the Channel scored a direct hit. One nurse was killed outright and the other received a perforating wound of the left eye. This iris prolapse was abscised and the wound healed. A traumatic cataract developed over the next year or so and eventually she was given a pension of 15s. a week by way of compensation. She subsequently married, gave up nursing, and had two children, but she found life as a one-eyed person rather trying, and her children did not hesitate to tease her, sometimes unkindly, about her disability.

When first seen 13 years later, at the age of 44, she had an inferior iris coloboma with a traumatic cataract. The cataract was extracted intracapsularly with some difficulty, because the lens capsule had become adherent to the limbal scar below. Three months later an anterior-chamber implant was inserted. The patient now sees 6/6 with a small correction, and has full binocular vision. In this case the patient was always psychologically well adjusted and no great change in her morale is yet noticeable; possibly her long contact with the medical profession has made her view the achievements of surgery with a certain scepticism, and perhaps she wonders if this happy result will last.

Discussion

The above examples suggest that it is possible to restore useful visual function to cases of uniocular aphakia many years after the original injury and at the same time to effect a notable improvement in the psychological well-being of the patients. It would clearly be better if such injuries were corrected in this way before amblyopia, squint, and psychological damage had appeared. The purpose of the operation, and the fact that it is proposed to insert a foreign body into their eyes, must, of course, be made clear to the patients, but in my experience the large majority of those with uniocular aphakia are very conscious of their disability and are not deterred by references to the experimental nature of this work. They want an improvement in their vision as soon as it can be arranged, and are not concerned at the possibility of complications, either immediate or delayed. Two of the patients in this series were so unhappy with their almost useless eyes that they requested that these be removed should they be considered unsuitable for implant surgery.

Summary

The rationale of the treatment of uniocular aphakia by means of anterior-chamber implants is described.

The first 100 cases treated at the Southend General Hospital are reviewed; the immediate results are regarded as satisfactory.

Another 5 to 10 years must elapse before the long-term results can be accurately assessed.

In the meantime, this operation can be offered with reasonable confidence to persons with uniocular aphakia who are worried by their disability and are anxious for treatment.

This piece of clinical research has entailed extra work for a busy department, and I am grateful to my colleagues, especially Dr. R. A. Owen, ophthalmic registrar, Dr. J. Alfred Lee, senior Anaesthetist to the Group, and to Sisters Cockerill and Gugarel, for their valuable assistance. The Southend-on-Sea Hospital Management Committee has been very understanding and helpful about the additional expenditure on this work, and as a result the extra funds have been made available without our having had to apply for or to obtain a grant in aid of this research. My thanks are also due to Rayner Ltd. for their close and helpful collaboration.

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ANTE-PARTUM MECONIUM STAINING OF THE LIQUOR AMNII

BY

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The discovery of meconium staining in the liquor amnii before the onset of labour raises a problem in management, and this paper is an account of the results obtained when an expectant course is adopted in the large majority of cases.

Meconium staining of the liquor amnii in labour has long been regarded by obstetricians as an adverse sign so far as the foetus is concerned; indeed, meconium appearing in liquor which had been clear earlier in labour is perhaps the most absolute sign of foetal distress. Lister and Buchanan (1957), in an investigation of the signs of foetal distress, found that of all single factors the passage of meconium gave the worst prognosis for the foetus. In their series the babies in 50% of the cases in which meconium was passed showed some signs of asphyxia at birth. For the purposes of their investigation they regarded a baby as asphyxiated if it did not cry within one minute of birth. The findings of Lister and Buchanan are in agreement with those of FitzGerald and McFarlane (1955).

Another view is that of Desmond *et al.* (1957), who considered meconium to be a marker for hypoxia and evidence that the foetus may become dangerously hypoxic during the remainder of the birth. In their series meconium was passed in 10.9% of cases: in these cases 77.2% of the babies had no difficulty in breathing at birth and in 22.8% there was difficulty of varying degree. This latter figure represents a threefold increase over a control series of cases. In conclusion, these authors stated that meconium staining of the liquor amnii does not imply that the foetus is in extreme distress but rather is close to its tolerance limits. Burger *et al.* (1956) studied the effect on the foetus of the intrapartum passage of meconium in 172 cases. In 79 of them no cause for the passage of meconium was found, and they thought that the passage of meconium by itself was not significant other than that it was an alarm signal.

Ante-partum meconium staining is discussed in the Blair-Bell Memorial Lecture given by J. Walker in 1954 and by Macafee and Bancroft-Livingstone (1958). Walker stated that meconium staining in the liquor was due to a deficient oxygen supply to the foetus, and that the saturation of oxygen in the umbilical vein was at or below the critical level of 30% Death from anoxia is preceded by meconium staining of the liquor for a variable period of time. On these grounds Walker urged the performance of caesarean section when heavy meconium staining of the liquor is encountered at artificial rupture of the membranes, and this was particularly indicated in primigravidae over the age of 30, since in these cases the incidence of prolonged labour is relatively high. Walker further stated that observation of the foetal heart was not a good guide, as frequently it stops suddenly without any period of slowing or irregularity. Macafee and Bancroft-Livingstone disagree with Walker's views and believe that the appearance of meconium is a danger which has been overemphasized.

Analysis of Cases

Artificial rupture of the membranes as a means of inducing labour is carried out in about 15 to 20% of cases admitted to Bellshill Maternity Hospital, and I have analysed a series of cases covering the three-year period 1955–57. In this period 2,054 surgical inductions of labour were performed, and in 125 of these the liquor was found to be meconium-stained—an incidence of just over 1 in 16 cases. There were 51 primigravidae and 68 multiparae in the series.

When meconium staining of the liquor is encountered the management is as follows. Any change in the foetal heart rate as a result of the induction is noted. Note is also taken of factors such as the patient's age, parity, and obstetric history. In some cases a decision to perform immediate caesarean section may be taken where there has been a significant alteration in the foetal heart rate or where other factors such as a bad obstetric history or severe toxaemia of pregnancy are present. In most cases, however, an expectant policy is pursued. The foetal heart rate is charted at 15-minute intervals for a few hours after the surgical induction; if, however, there is no alteration in the heart rate then charting is not continued to the interruption of the patient's sleep but is restarted at the onset of labour and continued until delivery.

In this series there were nine stillbirths and one neonatal death. This represents a perinatal mortality rate of 8%. The corrected rate is 2.4%, as in seven of the cases the foetus was abnormal—five cases of anencephaly, one case of hydrocephaly, and one case of hydrops foetalis. If another case in the series in which the baby was alive at the end of a month but had a severe degree of spina bifida is considered then the incidence of an abnormal foetus in association with ante-partum meconium staining of the liquor is the high figure of 6.4%.

With regard to the remaining stillbirths, one occurred in a primigravida who developed a severe mixed accidental haemorrhage. The second case was that of a gravida-2 aged 32 in whom labour was induced at the 41st week of pregnancy on account of prolongation of pregnancy. The latent interval before the beginning of labour was 20 hours 40 minutes and labour lasted four hours five minutes. The foetal heart was said to have disappeared suddenly in early labour, but on investigating this case it appeared that there was a vital gap of one hour in which the foetal heart was not recorded, and it may be that this stillbirth would have been prevented had the failure to maintain the foetal heart chart not occurred. Nevertheless, it cannot be said that in this case the foetal heart did not stop suddenly; but, even assuming that it did so, it still represents an incidence of less than 1%.

The one neonatal death that occurred was said to be due to asphyxia, and at the post-mortem examination plugs of meconium were found in the bronchi. The mother was a gravida-2 aged 22 in whom labour was induced a few days before term on account of rhesus iso-immunization. The latent interval before the onset of labour was 18½ hours and labour lasted three hours. The baby, which weighed 9 lb. (4.1 kg.), was delivered spontaneously, but was very cyanosed at birth and remained so in spite of resuscitative measures. It died after 6¼ hours. Study of the foetal heart chart in this case revealed that, although the foetal heart rate remained regular, there was an increase in rate from 120 to 160 beats a minute.

The number of caesarean sections performed in these 125 cases was 20, which is a caesarean section rate of 16% as against the hospital rate of 7.9%. In 13 of these cases the patients were primigravidae, while in a further three the only previous pregnancies had been abortions. Eleven of the women were not in labour. In the nine cases in labour the indication for caesarean section was foetal distress as evidenced by slowing or alteration of the foetal heart rate; foetal distress was also the indication for six of the cases not in labour. Severe pre-eclamptic toxaemia was the main indication in four of the other cases not in labour, while accidental haemorrhage was the indication in the remaining case. There was no foetal mortality among the cases delivered by caesarean section.

Eighteen cases in the series were delivered by forceps, representing a rate of 14.4% as against the hospital rate of 8.3%, so that again the rate for the series is almost double the hospital rate. None of the 18 babies was lost. In nine cases forceps were used solely on account of foetal distress, and in eight there was second-stage delay, due usually to a deep transverse arrest or to a persistent occipito-posterior position of the vertex. The remaining case was a patient in whom mitral valvotomy had been performed during pregnancy. Eleven of the cases were primigravidae and seven were multiparae.

Operative delivery was performed in a further six cases. Four were assisted breech deliveries, one was a case of twin pregnancy in which both babies required manual breech delivery, and the remaining case was that of a hydrocephalic foetus where craniotomy and forceps delivery were performed.

There were 81 spontaneous deliveries in the series. Foetal distress, therefore, necessitated operative delivery in 24 cases out of 125 (19.2%), and this gives a rough indication of the risk these infants run.

The antenatal history of these cases has been investigated to see if there was any anoxia that might have produced temporary foetal distress, but there were only seven cases in which a possible relevant factor was found. In two cases external cephalic version under general anaesthesia was performed, while in another two cases version was attempted but was unsuccessful. One case had had mitral valvotomy performed during pregnancy, while two other cases had suffered from severe anti-partum anaemia—that is, haemoglobin of less than 50%. In a further two cases the cord was tightly round the neck of the foetus at birth, but the significance of this is doubtful. Shui and Eastman (1957) concluded that cord round the neck was not of significance as a cause of foetal distress, but Reiss (1958) feels that it is a factor of importance, late in labour at least.

The indications for which induction of labour was performed were next considered, to determine if there was any particular group of cases in which the foetal risk appeared to be high. As might be expected, prolongation of pregnancy was the principal indication in 75 cases. Thirteen of the 20 caesarean sections and 12 of the 18 deliveries by forceps were in this group, but these figures are in proportion and do not represent an unduly high incidence. Toxaemia of pregnancy was the indication in 17 of the cases, but five of the caesarean sections and three of the forceps deliveries were in this group. Although the total number of cases is small the number of caesarean sections is slightly higher than one would expect. Whether this high rate in toxaemia is justified is questionable, but it was felt that the combination of severe toxaemia and meconium-stained liquor was a particularly unfavourable one for the foetus. The remaining groups were small and no worthwhile conclusions can be drawn from them, but the various indications were: rhesus iso-immunization, contracted pelvis, previous caesarean section, antepartum haemorrhage, foetal abnormality, unstable presentation, severe late vomiting of pregnancy, and breech presentation.

There were 117 babies born alive in this series, and in only one case did the baby show signs of serious asphyxia at birth which necessitated admission to the sick nursery. This was the baby which eventually died 6¼ hours after birth. In no other case did the baby have a degree of asphyxia severe enough to necessitate admission to the nursery. Milder degrees of asphyxia undoubtedly occurred, but in a retrospective analysis such as this it is impossible to make an accurate assessment from the records, since there were a number of observers and no fixed standard of asphyxia which would permit a more detailed estimate.

It is also impossible to form any estimate of whether the degree of meconium staining gives an indication of the foetal prognosis, as there were several observers and again a definite standard is difficult to set up. This point requires further elucidation.

Discussion

Meconium staining of the liquor calls for a careful assessment of the case, with a study of all relevant factors such as maternal age, parity, obstetric history, reason for the induction of labour, and any associated toxaemia. In the absence of any specially unfavourable combination of these factors an expectant policy seems justified by the results obtained in this series. Nevertheless, such cases require to be watched very carefully, and the organization should be so directed that the initial warning signs of foetal distress will not be missed, as the appearance of these calls for immediate delivery. It follows that all such cases should be observed in an institution where caesarean section or forceps delivery can be quickly and easily performed.

In discussing the observation of these cases the papers of Lister and Buchanan (1957), and of De Soldenhoff and Brill (1954) on foetal distress are of interest. Lister and Buchanan concluded that if the major foetal heart changes are awaited the opportunity for active intervention may already have been lost. For this reason the lesser deviations in a foetal heart rate from a sustained level must also be considered in determining treatment, as they carry a significant increase in the incidence of asphyxia at birth. Variations in the foetal heart rate of 20 beats a minute or more may be significant in these cases. De Soldenhoff and Brill mentioned the importance of a foetal heart chart, as it is not the isolated reading that is so vital but the observation of a series of heart rates over a period which gives a more accurate picture. They also noted that the slowing of the foetal heart rate during a contraction was a warning sign of early foetal distress and not a normal finding.

The avoidance of prolonged labour in these cases is important. In this series the latent interval between the induction of labour and the onset of labour varied between 15 minutes and seven days, but there does not appear to be any relationship between the length of the latent interval and the length or type of labour which followed. In the case in which the latent interval was 7 days, labour lasted 7¼ hours and ended in delivery by forceps on account of foetal distress; while in another case, in which the latent interval was only 2 hours, labour lasted 47¼ hours and also ended in delivery by forceps. The length of labour has been investigated in the 114 cases which were treated expectantly at first, and it is significant that labour was completed in 24 hours in 80% of them. Lister and Buchanan showed that the incidence of foetal distress and asphyxia increased directly with the length of labour, and it may be that the good results in this series are in part due to the fact that labour was short in a high proportion of cases.

Conclusion

When meconium staining of the liquor is found at artificial rupture of the membranes an expectant policy is justified, but the presence of meconium is an alarm signal which calls for a careful assessment of the case by the obstetrician in charge, followed by unremitting vigilance to detect the early signs of definite foetal distress which would necessitate immediate delivery. A more radical policy as advocated by Walker does not appear to be necessary, since some warning of foetal distress by alteration in the foetal heart rate is invariably given. It should further be borne in mind that there is a considerable chance that a foetal

abnormality may be present and that a conservative policy may avoid caesarean section in these cases. The avoidance of prolonged labour is also important, and cases in labour longer than 24 hours call for reassessment if delivery is not imminent.

Even when an expectant policy is pursued, however, a high number of operative deliveries will still occur, so that these cases require the resources of a specialist maternity hospital. While this is in agreement with the views expressed by Macafee and Bancroft-Livingston, the problem of ante-partum meconium staining would seem to be more serious than they admit, since 19.2% of the cases in the present series required to be delivered by caesarean section or by forceps on account of foetal distress. It is not known whether serious asphyxia at birth is responsible for any impairment in subsequent mental ability, but there is much to be said in these cases for the view expressed by De Soldenhoff and Brill that the early signs of foetal distress must be observed and acted upon if maximum foetal salvage is to be secured.

Summary

Different views on the importance of meconium staining of the liquor amnii are presented, and a series of 125 cases in which ante-partum meconium staining was encountered is analysed.

An expectant policy is justified in most cases, but the incidence of foetal distress is greatly increased, as operative delivery was required on this account in 19.2% of cases.

Both the caesarean section rate and the forceps rate in the series were twice the hospital rate. These cases therefore require the resources of a specialist maternity hospital.

The importance of the recognition of the early signs of foetal distress in these cases is emphasized, as is also the avoidance of prolonged labour.

It is also noted that there is an increased incidence of an abnormal foetus in association with ante-partum meconium staining.

I thank Dr. R. A. Tennent for his advice and criticism in the preparation of this paper.

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THE SCHULTZ–DALE ANAPHYLACTIC TEST FOR CARCINOMA ANTIGEN

BY

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Makari and Huck (1955) and Makari (1958) have reported that a carcinoma antigen could be detected in the blood plasma of carcinoma patients. To dectect the antigen they used the anaphylactic response of uteri from appropriately sensitized guinea-pigs described by Schultz (1910) and Dale (1913). Burrows (1958) has confirmed these findings. The work described below was an attempt to repeat these experiments.

Method

Human carcinomata were obtained at operation, and extracts were prepared as described by Makari and Huck (1955) and Makari (1956, personal communication). Homogenates were made in a rotary blender run at approximately 15,000 r.p.m. for 30 minutes, the blending container being packed in ice. They were then centrifuged at 3,000 r.p.m. (950 *g*) to remove debris. The supernatant from this centrifugation was recentrifuged at 10,000 r.p.m. (10,200 *g*) for 45 minutes, the precipitate being collected and stored at −20° C. This was the antigen to which guinea-pigs were to be sensitized.

Following the method of Makari and Huck, adjuvants were used with the object of increasing the sensitizing power of the antigen. The following modification of Freund's adjuvant was used:

"Bayol F"	.. .. ..	8.5 ml.
"Arlacel A" special	.. ..	1.5 ml.
Mycobacterium tuberculosis	..	5 mg. (steam-killed desiccated human bacilli)

These ingredients were mixed, an equal volume of a 20% suspension of antigen was added, and an emulsion was made in a glass blender.

Young virgin female guinea-pigs were given 1 ml. each of the emulsion by multiple subcutaneous inoculation. They were used for sensitivity tests between three and six weeks after inoculation.

Blood plasma for testing was obtained from patients with carcinoma and from normal subjects by venepuncture. A nylon syringe was used, and subsequently the blood and plasma were handled entirely in "polythene" or in siliconed glassware. Dry heparin was added and the blood cells were removed by centrifugation as soon as possible. The plasma was stored at +4° C. for one to four days and was then divided into small samples, each sufficient for one test, and frozen to −20° C. It was allowed to thaw at room temperature just before it was needed. In the last two series of experiments the plasma was dialysed in "cellophane" against normal saline at +4° C. for 24 hours, and soya bean trypsin inhibitor (S.T.I.) was added at a concentration of 1 mg./ml. before the plasma was frozen.

Blood plasma for desensitization of the uterus preparations was obtained from the human blood bank. Group O rhesus-positive blood was used. After removing the blood cells this plasma was also frozen

in small portions. Any plasma tinted pink through haemolysis was discarded.

For the anaphylactic test, a horn, or part of a horn, of the uterus of a sensitized guinea-pig was mounted on an isolated organ bath of 2 ml. capacity, filled with half-calcium Tyrode's solution (composition: NaCl 8 g./l.; KCl, 0.2 g./l.; $CaCl_2$, 0.1 g./l.; $MgCl_2$, 0.01 g./l.; $NaHPO_4$, 0.05 g./l.; $NaHCO_3$, 1 g./l.; dextrose, 1 g./l.). The solution was oxygenated and kept at 37° C.

As control, an unsensitized horn was similarly mounted and treated in exactly the same way as the sensitized one throughout the test. Movements of the muscle were recorded by levers writing on a smoked drum. The experiment was duplicated, using two parts of each uterus in separate baths. The horns were first desensitized to the normal constituents of human plasma by the group O plasma. When the first dose of 0.1 ml. of plasma was given, a large contraction of the sensitized preparation always occurred within half a minute.

After washing out with fresh solution, a successive dose usually produced less response, and this was repeated until no further response was obtained. In later experiments this process was curtailed by giving a larger initial dose (0.5 ml.) of the desensitizing plasma.

When desensitization was complete, 0.1 ml. of the plasma to be tested was added to the bath. A contraction of the sensitized horn of one-fifth or more of maximal size, and occurring up to five minutes after the addition of the test plasma, was said by Makari and Huck to indicate the presence of carcinoma antigen in the plasma. If the unsensitized preparation also contracted, it was said that an unwanted contracting substance had formed in the plasma.

Results

During the four series of tests 42 guinea-pigs were sensitized, using antigen from a pool of five mammary carcinomata and from five separate carcinomata of colon or rectum. Freeze-dried pooled antigen from six other carcinomata of colon or rectum were also used. Of the 64 preparations of sensitized uterine muscle set up, 13 failed to become satisfactorily desensitized to group O plasma and were excluded from the tests.

In the first two series of experiments plasma samples were collected from seven carcinoma patients. Four of these samples were pooled, but the other three were used separately. These plasma samples produced contractions in 19 out of 34 sensitized preparations and in 13 out of 28 control preparations. Although the sensitized preparations contracted more often than the control preparations, the difference is not statistically significant ($\chi^2=0.26$; for $n=1$). The pooled plasma and one of the separate samples contracted the preparations with which they were tested less frequently than the other two samples, but every plasma contracted some of both the sensitized and the control preparations. Plasma was also taken from one healthy subject. This contracted five out of seven preparations with which it was tested.

In the second two series of experiments, plasma was taken from three carcinoma patients and three normal subjects, and unwanted contracting agents were eliminated by dialysis and the addition of S.T.I. Plasma from the carcinoma patients was tested with 17 sensitized preparations and produced no contractions. Plasma from a normal subject was also used with each of these preparations, and produced no response. The dialysed plasmas had no effect on any of six unsensitized preparations. However, a portion of one of the samples from a normal subject was treated as in the earlier experiments, and was found to possess strong contracting activity with both sensitized and control preparations.

There was great variation between the sensitivities of different uteri and even of the different parts of the same uterus. Different parts of the same uterus gave conflicting results with portions of the same plasma sample in 12 experiments. Further, on no fewer than six occasions the unsensitized preparation contracted in response to a test dose of plasma which had no effect on the sensitized preparation for which it was the control.

It was a further difficulty that the uterine muscle often underwent spontaneous contractions, and these were sometimes large and irregular even though the half-calcium Tyrode's solution recommended by Dale was used throughout the experiments. The contractility of the preparation as evidenced by this spontaneous activity, and by the responses to desensitizing doses of group O plasma, did not differ appreciably between experiments conducted in January and in August.

Discussion

Though reproducing as faithfully as possible the conditions laid down by Makari and Huck, it has not been possible to demonstrate carcinoma antigen in the plasma of patients with carcinoma.

Guinea-pigs were sensitized using antigen derived from a number of carcinomata of rectum and colon, which were said by Makari and Huck to be a good source of antigen, and from several carcinomata of the breast, which Burrows considered equally satisfactory. Since all the inoculated guinea-pigs appeared to become strongly sensitized to the normal constituents of human plasma, it seems that a fault in the technique of sensitization was unlikely to be responsible for our failure to elicit an anaphylactic response to carcinoma antigen.

The appearance of unwanted contracting agents in the plasma samples constituted a major difficulty. Makari and Huck stated that they could eliminate these substances from their samples of plasma by handling them entirely in "non-wetting" containers and by storage for 24 hours at +4° C. before freezing. Burrows only found it necessary to prevent haemolysis. However, in our experience, blood plasma taken from both carcinoma patients and normal subjects which had been handled with these precautions often contained substances that caused the muscle of the guinea-pig uterus to contract, whether sensitized to carcinoma or not.

The method of desensitization used by Makari and Huck and by Burrows was found by them to require repeated doses of group O plasma, and this was confirmed in the present experiments. In contrast, the uteri of three guinea-pigs highly sensitized to egg albumen were found to be completely desensitized to this antigen after a single dose only just sufficient to

elicit an anaphylactic response. This is in accord with the original work of Dale (1913), who showed that only when uterine muscle was too thick for rapid penetration by the antigen could a second dose produce even a weak anaphylactic response. In the present investigation the thickness of the muscle was unlikely to be important, since the guinea-pigs were young virgins and their uteri were small. It does not seem likely that the sensitivity elicited to the normal antigens of human plasma by following the method of Makari and Huck would be materially different from the sensitivity which can be elicited to their antigens. It is possible, therefore, that the repeated contractions produced by successive doses of group O plasma were not purely anaphylactic responses, and that the apparent desensitization which was achieved was not due to anaphylactic desensitization.

Besides the contracting substances like histamine and 5-hydroxytryptamine likely to be formed in blood and plasma which is being handled, Schachter (1956) has described a slow contracting effect which manifests itself one-half to three minutes after serum or plasma has been diluted in Tyrode's solution. He considered that a substance was formed by an enzyme system which was activated on dilution. This phenomenon may well have accounted for many of the contractions seen in the present experiments, since 60% of them were delayed for half a minute or longer. The method described by Makari and Huck was considered by Schachter (1956, personal communication) to be suitable for the demonstration of this delayed activity, since the dilution of plasma in the Tyrode's solution was of the correct order, and a contraction which was delayed even for five minutes was to be accepted as a positive result. Unfortunately Schachter also reported that the delayed effect in human plasma is unpredictable and not easily inhibited. However, it was thought that S.T.I. at a final concentration of 50 μg./ml. might suppress the enzyme system sufficiently for the purposes of the experiment.

This concentration of S.T.I. has been shown by Mongar (1956) not to inhibit appreciably the liberation of histamine from guinea-pig lung by anaphylaxis. Schachter also advises dialysis to ensure the elimination of small-molecule contracting substances formed in the plasma during its early handling. Burrows and Neill (1958) have stated that dialysis did not remove the antigenic fraction from his samples of serum.

Although these precautions were effective in eliminating contracting activity from the plasma samples, still no carcinoma antigen could be detected.

In addition to the difficulties experienced, due to the frequent detection of contracting agents in the plasma samples, the responses of the uterine muscle preparations to these pharmacological stimuli were erratic. Makari and Huck, and Burrows, considered the reactions of a single sensitized preparation, with its control, to be adequate to demonstrate the presence of carcinoma antigen in a sample of plasma. But we found that the unpredictable sensitivity of the preparations to other stimuli, and their frequent high level of spontaneous activity, made it impossible to attach this significance to the result of a single experiment.

The findings in the present experiments differed from those of Makari and Huck and of Burrows on three other points. (1) Burrows reported that a large proportion of his inoculated guinea-pigs failed to become sensitive, even to the normal group O plasma. (2) He found it necessary to give the animals oestrogens during the winter to ensure that their uteri would be contractile. Although young guinea-pigs were used, neither of these difficulties was met with in our experiments. (3) Neither Makari and Huck nor Burrows detected the slow contracting substance described by Schachter. Since they took no precautions which would have eliminated it, the sensitivity of their preparations to this stimulus was probably low.

Summary

An attempt has been made to repeat the experiments described by Makari and Huck (1955) for the detection of carcinoma antigen in the plasma of patients suffering from carcinoma.

Carcinoma antigen was not demonstrated.

It was found that the precautions advised by Makari and Huck did not prevent the frequent appearance of contracting activity in the plasma samples, probably due to pharmacological agents. The conditions of the experiment were suitable for the demonstration of the slow contracting effect described by Schachter (1956).

This difficulty was avoided by dialysis of the plasma samples and the use of soya bean trypsin inhibitor.

I thank Dr. J. L. Mongar, who kindly allowed me to use his laboratory in the Department of Pharmacology, University College, and has given me much help and encouragement; and Dr. M. Schachter for his criticism and advice. My thanks are also due to a number of my student colleagues of University College Hospital who helped greatly during the earlier experiments. I am indebted to the surgeons at University College Hospital, the Princess Beatrice Hospital, the Royal Marsden Hospital, St. Mary's Hospital, St. Thomas's Hospital, and the Westminster Hospital, who have provided me with carcinomata.

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Factory accidents reported in 1958 fell by 4% over the previous year to their lowest level for 23 years, according to the Annual Report of the Chief Inspector of Factories. The number reported fell from 174,713 in 1957 to 167,697, although fatal accidents rose slightly from 651 to 665. Although there was an increase in the number of fatal accidents in 1958 compared with 1957, the reduction of about 4% in the total number is a continuation of the downward trend in these figures during the last three years. The Chief Inspector regretted that in building operations and works of engineering construction there had been an appreciable rise in the accident figures. On building operations the total number of accidents in 1958 was 15,017, of which 207 were fatal, compared with 14,568 and 156 in 1957. On works of engineering construction the total for 1958 was 2,329 with 51 fatalities, and the corresponding figures for the previous year were 1,924 and 31. "Since there was no appreciable increase in the amount of work of this type in 1958 over that undertaken in 1957," the Chief Inspector remarks, "the figures can only be regarded as disappointing and clearly show the need for more positive action by the industries concerned." (H.M.S.O., Cmnd. 810, price 5s. 6d. net.)

HAEMOCHROMATOSIS IN A FAMILY, AND ITS OCCURRENCE IN TWO WOMEN

BY

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Haemochromatosis is an uncommon disease which occurs principally in men. Houston (1953) was able to review 512 reported cases, of which only 33 were women. A familial incidence of the disease is not well known, although its occurrence has been reported on a number of occasions (Sheldon, 1935; Lawrence, 1935, 1949; Rogers, 1950; Houston and Zilkha, 1955; Houston, 1957). In this paper a family is reported in which two brothers have haemochromatosis in classical form, and their sister, who has neither symptom nor sign of the disease, has a raised serum iron. Two female patients who have the classical triad of cirrhosis, diabetes, and skin pigmentation are also reported.

Case Reports

Case 1.—This patient was born in 1900. Symptoms of diabetes developed in 1950, but he did not receive treatment until 1951, when he was admitted to the Dumfries and Galloway Royal Infirmary in diabetic precoma. Enlargement of the liver was observed at this time and did not regress when his diabetes was stabilized. Skin pigmentation became obvious about three years later, but a skin biopsy showed no increase in iron. Skin pigmentation continued to increase, however, and by 1957 there was no doubt about the diagnosis. The liver was enlarged 5 in. (12.5 cm.) below the right costal margin and was firm. The skin had a slate-grey hue. Diabetes required 80 units of insulin zinc suspension for control. Serum iron was 554 μg./100 ml., but liver function tests were normal. Regular venesection was begun at this time and improvement has taken place.

Case 2.—Born in 1906, the brother of Case 1. He was admitted to hospital in 1957 complaining of weight loss and vague ill-health of one year's duration. He did not admit to thirst or polyuria, but the urine contained sugar, and a glucose-tolerance curve was typical of diabetes mellitus. On examination he was found to have slight skin pigmentation and hepatic enlargement to just below the right costal margin. Haemochromatosis might not have been considered had his brother not been known to the medical unit, for the signs were not striking. Serum iron, however, was greatly increased at 332 μg./100 ml., and regular venesection has been employed with benefit and without the occurrence of anaemia. His diabetes is controlled by diet alone. Liver-function tests are normal.

Case 3.—Born in 1897, the sister of Cases 1 and 2. She was examined at my request and had no complaint other than joint pain due to long-standing rheumatoid arthritis. The only positive features on examination were related to the arthritis. She had six full-time pregnancies between 1920 and the early 1930's, and the menopause took place in 1947. The urine was free of sugar and liver-function tests were normal, but the serum iron was raised to 190 μg./100 ml. (normal range 78–170 μg./100 ml.).

Case 4.—A married woman born in 1897 developed diabetes in 1948 shortly after emigrating from Glasgow to South Africa. Her skin had always been dark, but it became much darker at this time. In 1950 she was admitted to the medical wards of the University of Witwatersrand in diabetic coma, and during this admission a diagnosis of haemochromatosis was clearly established by liver biopsy and radioactive iron studies. Diabetes was extremely difficult to control, and the daily dose of soluble insulin varied from 400 to 600 units. In 1953 she returned to Glasgow and was admitted to the professorial medical unit in the Royal Infirmary for stabilization of diabetes. The menstrual history, obtained at this time, was that periods had been scanty for many years and had ceased completely in 1947 at the age of 50. She had never been pregnant. On examination the liver was enlarged 2 in. (5 cm.) below the right costal margin and the skin was obviously pigmented. Serum iron was 248 μg./100 ml. and the serum iron-binding capacity was nil. Liver-function tests were normal. The patient has been treated most successfully over a period of eight years by repeated venesection, and signs of the disease have regressed. Insulin requirements, however, are still very high.

Case 5.—A woman born in 1892 was admitted to the Dumfries and Galloway Royal Infirmary in 1955 for stabilization of diabetes. She was found to have dusky skin pigmentation and hepatic enlargement of 3 in. (7.5 cm.). Serum iron was 379 μg./100 ml. and a glucose-tolerance curve was typical of diabetes mellitus. Liver-function tests were normal. The patient began to menstruate at the age of 10, and the menopause took place while she was in her early thirties. She had three sons, all of whom were stated to be well, but unfortunately none was available for examination. Treatment by repeated venesection has been successfully carried out.

Discussion

Haemochromatosis is due to an inborn error of metabolism whereby excessive amounts of iron are absorbed from the small intestine and stored throughout the body, notably in liver, spleen, marrow, pancreas, heart muscle, pituitary, and skin. Symptoms and signs of the disease are uncommon before middle life in men and generally occur at a greater age in women. Physiological loss of iron by menstruation and pregnancy is the accepted explanation for the paucity of female patients, but it is probable that this loss merely delays the recognition of haemochromatosis and that the fundamental abnormality of iron absorption is present in both sexes.

Assuming that the reproductive life of a woman extends between the ages of 13 and 50, and that the average menstrual loss each month contains 25 mg. of iron (Fowler and Barer, 1935), then approximately 11 g. of iron is removed from the body by menstruation alone, the approximate equivalent to the iron contained in 44 pints (25 litres) of blood. In addition, each pregnancy would account for a further loss of 0.5 g. of iron, even when allowance is made for the absence of the menses. These figures can be compared with the quantity of iron in the tissues of a patient with haemochromatosis, estimated to lie between 20 and 60 g. (Sherlock, 1955). It can therefore be understood how physiological iron loss will retard the progress of the disease, and it is probably significant that many of the reported female patients with haemochromatosis had absent or scanty menstruation. Houston (1953) could find only three female patients in whom a diagnosis was made before the age of 45 years, and one of these had had amenorrhoea for 13 years prior to her death.

In Cases 4 and 5 both patients have abnormal menstrual histories in that periods were abnormally scanty in Case 4, while in Case 5 the menopause occurred at a very early age. In the latter case haemochromatosis was not recognized until 30 years after menstruation had ceased. In Case 3 the patient, who had a normal menstrual history and a family of six, would appear to have so delayed the progression of the disease that, at

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the age of 61, she still has neither symptom nor sign, although the serum iron is raised.

Until recent years there was no effective treatment for haemochromatosis. The various therapeutic regimes, such as a low-iron diet, or a diet rich in phosphorus to delay the absorption of iron, met with little or no success; this was not surprising, as large quantities of iron had accumulated in the body by the time that the disease was productive of symptoms. The only rational method of effecting improvement is to remove iron from the tissues, and this can readily be achieved by repeated venesection, each pint (570 ml.) of blood containing about 250 mg. of iron. After venesection, mobilization of body iron is rapid, and 20 to 40 pints (11.4 to 22.7 litres) of blood can be removed in as many weeks without the development of a hypochromic anaemia. The good results of this treatment were first reported by Finch (1949) and have been confirmed by other workers (Davis and Arrowsmith, 1952; Finch and Finch, 1955; McAllen, Coghill, and Lubran, 1957). The recognition of a familial incidence of the disease will enable the diagnosis to be made in the relatives of such patients at a stage before the development of symptoms. If a raised serum iron is accepted as evidence that haemochromatosis exists in a subclinical form, treatment by controlled venesection may prevent the occurrence of clinical disease. It is therefore important to examine the relatives of these patients and to make periodic estimations of their serum iron.

During the past six years, as part of a study of portal cirrhosis, I have been interested in eight patients with haemochromatosis. Three of these patients had duodenal ulceration of some severity. One man presented with a perforated ulcer; a second man died from haemorrhage when a large chronic ulcer eroded an artery; a third man had a 20-year history of chronic dyspepsia, and cirrhosis was first observed when a gastrojejunostomy was performed. This association has not previously been commented on, although four of the seven male patients with haemochromatosis reported by McAllen, Coghill, and Lubran (1957) also had duodenal ulceration. Sheldon (1935) cited only one instance of this in his review of 311 cases. It is possible that this observation is but a reflection of an increasing incidence of duodenal ulceration in men during the twentieth century, but the occurrence is reported here as it may have some relevance, particularly as the duodenum is believed to be the principal site of iron absorption.

Summary

The cases of two brothers with haemochromatosis are reported. Their sister, aged 61, has a raised serum iron but is at present asymptomatic. As repeated venesection may halt the progress of this disease, it is suggested that the relatives of patients with haemochromatosis should be examined and serum iron estimations made.

The cases of two women with classical haemochromatosis are reported. In both instances the diagnosis was made after the menopause.

The occurrence of duodenal ulceration in three out of eight patients with haemochromatosis is commented on.

I thank Dr. James Laurie and Professor L. J. Davis for their helpful advice and for permission to publish the case reports. I also thank Dr. Ian A. Anderson, of the Victoria Infirmary, Glasgow, for the serum iron estimations on Cases 1, 2, 3, and 5.

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"LIPOSTABIL": A PILOT STUDY

BY

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A number of preparations have been introduced recently for the treatment of diseases associated with abnormal lipid metabolism. Their purpose is to reduce abnormally high cholesterol levels and in other respects to restore a more normal blood lipid pattern. These preparations are mainly intended for the treatment of patients with ischaemic heart disease, and this report gives the results of a pilot trial with one of them ("lipostabil"). Each capsule contains: alpha- and beta-lecithins of soya bean, 175 mg.; 3-4-5 polyoxyethylene-sorbitolmono-oleate, 100 mg.; potassium theophyllinate potassium thiocyanate, 50 mg.; (addition compound).

Material and Methods

Ten patients with ischaemic heart disease were studied, and in most of them the disease was severe. One died, and a second developed severe congestive failure, so that our results relate only to the remaining eight patients. Details of these are given in Table I. Four had an abnormally high serum cholesterol (more than 340 mg./100 ml.), while the other four had wide pre-beta-lipoprotein bands (Besterman, 1957). The width of these bands has been expressed arbitrarily as 0–3 (Smith, 1957). In addition, two of these patients had xanthomatosis tendinosum and a third had xanthelasma.

TABLE I.—*Details of Cases*

Case No.	Age and Sex	Condition Present	Initial Cholesterol (mg./100 ml.)	Width of Pre-beta Band
1	M 59	Myocardial infarction and angina	263	2
2	M 46	" " "	267	2
3	M 55	" " "	264	2
4	M 50	Angina	278	1
5	F 53	Angina; xanthelasma	500	1
6	M 44	Myocardial infarction; xanthomatosis tendinosum	385	½
7	M 56	Angina; xanthomatosis tendinosum	485	½
8	M 66	Angina	368	0

Blood samples were taken in the morning between one and two hours after a light fat-free breakfast.

Serum cholesterol was estimated by Abell's method (Abell *et al.*, 1952); but instead of slow centrifuging to separate the ethereal and aqueous layers the tubes were left to stand at room temperature for 20 to 30 minutes.

Paper electrophoresis was carried out by the method described by Flynn and de Mayo (1951). 0.15 ml. of serum was applied to a 3-in. (7.5-cm.) strip of Whatman No. 3 filter-paper. Strips were run for 17 hours (overnight) at ½ mA/in. Each strip was unequally divided, the narrower part being stained for protein with light-green dye and the broader for lipids with Sudan black.

Results

Most of the patients were already taking a diet restricted in fat, and no changes were made over the period of observation. Several patients showed minor fluctuations in weight, but in none was there any consistent or progressive change.

The initial dose of lipostabil was 4 or 5 capsules a day, one being taken after a small uncooked meal, and two after a larger cooked meal. For the second month the dose was increased, and for the third month it was again increased up to the limit of tolerance (usually 8 to 11 capsules a day).

Cholesterol.—Four cholesterol values were obtained at weekly intervals before starting treatment, and the later results are expressed as a monthly average (Table II). As will be seen, there was a slight

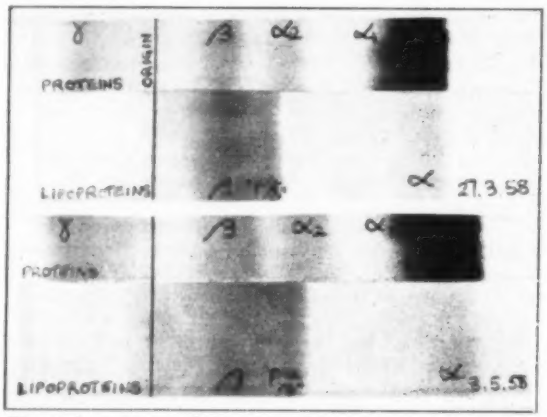
TABLE II.—*Serum Cholesterol (mg./100 ml.)*

Weekly Cholesterol During Control Period	First Month	Second Month	Third Month	After Stopping Treatment
351–340–344–345	335	328	312	317

progressive fall over the three-months period. However, the average value one month after stopping treatment was also lower than the control figures. There is no evidence that the effect of lipostabil can persist for some weeks after stopping treatment, and it is possible that this change might be part of a seasonal variation in diet or activity. But, in any case, the reduction was less than would be required of an effective therapeutic agent. The capsules contain linoleic acid, which is known to be of value in reducing serum cholesterol levels in man, and such reduction is related to the amount of linoleic acid given. However, the dose of lipostabil is limited by side-effects, particularly gastric upset, probably due to the theophylline, so that in practice an effective fall in cholesterol could not be achieved. Another common side-effect was constipation, but this was not as troublesome as the gastric symptoms.

Pre-beta-liproprotein.—There is at present no satisfactory way of expressing the size and density of this band as an exact mathematical measurement, but the width has been recorded according to the grades proposed by Smith (1957). Any improvement, therefore, had to be assessed visually, but, though there were minor changes in several patients, none showed any progressive or consistent change (see Fig.).

Clinical Assessment.—The lesions in the patients with xanthomatosis and xanthelasma were photographed during the control period and comparison between these photographs and the lesions at the end of the period of



Electrophoretograms of the serum of a man age 55 before and after treatment with lipostabil for six weeks. The control strip shows a heavy pre-β band, and the pattern in the second strip is identical.

treatment showed no change. In two of the eight patients who completed three months' treatment the angina became more severe, in one it improved, and in the other five there was no change.

Summary

Ten patients with ischaemic heart disease and well-marked lipid disturbances were treated with lipostabil. Although the dosage was increased to the limits of tolerance no satisfactory fall in blood cholesterol was obtained. The liproprotein pattern, studied by electrophoresis, and in particular the pre-beta band, was unchanged.

The clinical course of these patients was what could be expected from the natural history of this disease.

We thank Mr. F. R. J. Donner, of John Ronaldson & Co. Ltd., for providing the lipostabil, and Dr. Paul Wood for advice and encouragement.

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Medical Memoranda

Unusual Case of Congenital Pyloric Stenosis

The case described presented some unusual and interesting features which make it worth recording.

Case Report

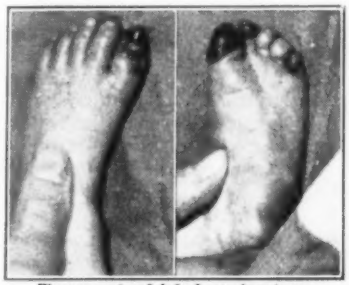
A male first-born infant was delivered by caesarean section because of cephalo-pelvic disproportion. His birth weight was 7 lb. (3,175 g.) and he gained weight slowly but steadily till 14 weeks, when he weighed 11 lb. 5 oz. (5,130 g.) and appeared a normal baby.

He was admitted to hospital on March 9, 1956, at the age of 15 weeks with a history of vomiting for 10 days. The vomiting followed every feed, contained "coffee-grounds" material, and was non-projectile. Melaena stools had been passed on two occasions; at other times the stools had appeared normal.

On examination he weighed 9 lb. 14 oz. (4,480 g.) and was very pale. No abnormality was noted in the abdomen or elsewhere. The haemoglobin was 58%, red cells 2,840,000 per c.mm.; the white-cell count, differential count, platelet count, bleeding-time, and clotting-time were normal.

The vomiting continued, sometimes forcibly and sometimes containing altered blood. Several melaena stools were passed and the haemoglobin fell to 26%. There was an intermittent fever. A blood transfusion was given via a cannula tied into the long saphenous vein anterior to the medial malleolus at the left ankle, and on March 12 a laparotomy was performed (Mr. A. Jolleys). The stomach was dilated and a pyloric tumour was palpated. A Ramstedt operation was done. No other abnormality was found in the abdomen. The intravenous drip was discontinued after 24 hours, by which time 230 ml. of blood, 200 ml. of 4.3% dextrose in 0.18% saline, and 2 mg. of tubocurarine had passed through the cannula.

Subsequent progress was complicated by the continuation of a low-grade pyrexia, without obvious cause except for slight redness around the drip wound. For this reason penicillin and streptomycin were given intramuscularly for six days into both thighs and buttocks. Four days after operation the whole of the skin of the left lower limb below the mid-thigh became cold and "marbled" (blotchy cyanosis alternating with pallor). A black blister appeared on the great toe, and obviously there was circulatory inadequacy despite the fact that femoral, posterior tibial, and dorsalis pedis pulses were palpable and equal on the two sides. After a further three days a line of demarcation appeared across the proximal phalanx of the great toe and a purple spot of superficial skin gangrene on the second and fifth toes (see photographs). The "marbling" was by now inconstant and appeared particularly when the thighs were flexed with the infant in the sitting position.



Photograph of left foot showing superficial skin gangrene.

The infant slowly improved; the superficial skin gangrene of the second and fifth toes separated and healing occurred. After amputation of the distal and half of the proximal phalanx of the great toe, the wound readily healed.

The infant was discharged well on May 16 weighing 12 lb. 5 oz. (5,585 g.).

COMMENT

The onset of symptoms in this case was unusually late, the infant being normal until 14 weeks of age. Rendle-Short and Zachary (1955), stressing the rarity of onset after 12 weeks of age, were able to find only one such case in the literature and added two of their own. Congenital pyloric tumours can undoubtedly persist into adult life, when their discovery is usually an unexpected finding during the course of investigations into the cause of dyspepsia and peptic ulceration. Such cases rarely give a history of feeding disorders in infancy (Desmond and Swynnerton, 1957).

The vomiting of altered blood in pyloric stenosis is common, but obvious melaena and profound anaemia are very rare. Such extensive bleeding is more likely to be due to an associated hiatus hernia (I. Forshall, 1957, personal communication). However, in this case the cessation of vomiting after the Ramstedt operation and the inability to demonstrate a hernia or reflux by careful radiological screening would seem to rule out this possibility.

The other unusual feature was the complication of peripheral gangrene. Gangrene of the extremities in infancy falls into two fairly distinct categories. (1) The so-called "spontaneous" gangrene of the newborn, where the following factors are concerned: difficult labour, accidents of birth, including obstetrical procedures (Heller and Alvari, 1951); prematurity; cardiovascular anomalies (Gross, 1945); metabolic disorders such as diabetes (Lawrence and McCance, 1931); galactosaemia (Haas, 1955); infections such as syphilis (Foster and Taylor, 1949); displaced injections into the umbilical artery instead of the umbilical vein (Mills, 1949). (2) Those occurring after the first few weeks of life, the commonly associated conditions being infectious diseases (measles, diphtheria, etc.), anaemia, dehydration, local trauma, local sepsis, pink disease, arteriovenous fistulae, and mechanical causes.

In 1914 von Khautz was able to collect from the literature 50 cases of peripheral gangrene in children, 39 of them in association with infectious diseases. With improvements in the treatment and control of such disease the pattern has changed so that the other factors assume greater importance, but local and general infection remain major causes (Stokes and Shumacker, 1952). Miller and Sebeck (1955) described five cases of peripheral gangrene in infants following intravenous infusions via "cut-down" cannulization of vessels. In all five there were complications of the kind referred to, but the authors stress the importance of vascular spasm. Areas of necrosis of skin proximal to the site of "cut-down" drips are not uncommon (D. Browne, 1956, personal communication) but occurring distally they are rare.

In the present case the whole of the skin below the mid-thigh suffered from circulatory inadequacy despite the fact that the pulses were palpable and equal on the two sides at all times. The "cut-down" was performed according to accepted techniques, and bandaging of the immobilized limb was never overtight. The interval of four days between the removal of the cannula and the onset of skin changes makes it difficult to believe that the latter were due directly to the drip. It seems that a widespread, superficial, arteriolar spasm in the left lower limb is the best explanation for the observed changes—the anaemia, dehydration, operative and local trauma, local sepsis, etc., acting as adjuvants.

I thank Dr. T. N. Fisher for permission to publish this case, and Professor W. F. Gaisford for helpful advice and criticism. The photographs were provided by the department of clinical photography, Manchester Skin Hospital.

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Reviews

SOCIAL CONDITIONS IN ENGLAND

A Survey of Social Conditions in England and Wales as Illustrated by Statistics. By A. M. Carr-Saunders, D. Caradog Jones, and C. A. Moser. (Pp. 302+xxi. 25s.) London: Oxford University Press. 1958.

Although the risks of some of the major epidemic diseases were shared by all classes of society, it has always been fairly evident that people who were sick were frequently poor. It has not always been recognized that a considerable proportion of them were sick because they were poor. Until the nineteenth century it was possible to believe that those who were sick and poor were in some way intrinsically inferior, and that an improvement in their income would have little effect on their health, and perhaps only a temporary effect on their poverty. In preferring £5 which he would be happy to spend to £50 which he would be unhappy to save, Mr. Doolittle in Shaw's *Pygmalion* would have been regarded by some people as typical of a class for which little could be done in respect of health or wealth by public action.

To-day no thoughtful person questions that social conditions have an immense influence on health. To a considerable extent this change in viewpoint is attributable to the careful reporting of observers from Mead to Rowntree, and in title and content *A Survey of Social Conditions in England and Wales* deserves to be regarded as the latest contribution to a distinguished series. The task of describing the social scene is, however, very different now from what it was in the eighteenth and nineteenth centuries. At that time so little was known that almost any carefully documented statement was bound to be of interest. To-day there are few facets of social life which are not either reflected in national statistics or described by some crass observer, and to be of value a new book must either give more information than is available elsewhere to the research worker or develop a theme which will catch the attention of the general reader. This one does neither of these things. It attempts what the authors describe modestly as "the pedestrian task" of presenting "a coherent picture of some of the more important aspects of social life in England and Wales so far as they can be illustrated by statistics." The result is that the statistics are too few for the one purpose and too many for the other. The point may be illustrated by the treatment of the sex ratio. The data are inadequate for the research worker, who would have to consult other sources; yet the discussion of this fascinating subject is not one which would hold the attention of the general reader not already interested in it. Moreover, the statement that "the excess of males over females must be greater at conception than at birth" ignores the fact that until there is more information about the sex of early abortions the ratio at conception must remain an open question. In relation to the broad theme of the book the treatment of the sex ratio is perhaps a small matter, but it illustrates the difficulties presented by a statistical approach to so large a subject. It should be said, however, that within the framework of its own intentions the book succeeds admirably. It is the intentions about which one is doubtful.

THOMAS McKEOWN.

RESPIRATION

Handbook of Respiration. Analysis and compilation by Philip L. Altman, John F. Gibson, Jr., M.D., and Charles C. Wang. Edited by Dorothy S. Dittmer and Rudolph M. Grebe. (Pp. 403+xv; illustrated. 52s. 6d.) Philadelphia and London: W. B. Saunders Company. 1958.

This handbook provides in readily available tabular form a veritable mass of quantitative information on respiration—human, animal, and vegetable. The information has in most cases been assembled by a leading authority in each field, and a vast range of literature (predominantly American) is covered. It is impossible to list all the subjects dealt with. They range from basic physical and chemical properties of respiratory and anaesthetic gases, through tables of normal values of pulmonary function tests, to characteristics of haemoglobins and other respiratory pigments, the effects of drugs and various inhaled gases on respiration, and the effects of some diseases on pulmonary function. Information is given for human subjects and for many laboratory animals and even for plants. There is an enormous amount of useful information in this volume which is not readily acquired elsewhere, but the reader must be on his guard against assuming that it is complete or always accurate. There are some curiously futile little tabulations, such as a list of 18 causes of dyspnoea and a list of mechanisms of dyspnoea which makes no mention of exercise hyperpnoea, and some of the clinical sections are so superficial and incomplete as to be almost valueless. For the critical worker, however, this is a most useful source of information, and anyone working in the field of respiration should at least glance through it to see what it has to offer him.

C. M. FLETCHER.

INSPIRING RECORDS

Frontier Doctor. An Autobiography. By Sir Henry Holland. (Pp. 256; illustrated. 25s.) London: Hodder and Stoughton. 1958.

A Doctor's Story. By Sir Fred Bowerbank. (Pp. 341; illustrated. 30s.) Wellington: Harry H. Tombs Ltd. 1958.

These two autobiographies have many things in common. Both the authors are doctors, both trained in Edinburgh, both left their native land and lived most of their lives far from the land of their birth, both rose to great eminence in their very different spheres. There the similarity ceases, except that their widely differing experiences make most interesting reading.

Sir Henry Holland became a legendary figure in India as a medical missionary. His work as an ophthalmologist in Quetta and Shikarpur brought him immense fame. Fortune, too, was there for the taking, but not for Holland, whose whole life was dedicated to the service of the God he so faithfully served with no thought of self. A general surgeon of remarkable skill, he literally performed miracles, most frequently under very primitive conditions. In these days of "Records," when nitwits try to crowd into telephone booths, it will be a long time before 4,000 patients are seen and 500 operations, including 203 cataracts, are again performed in three weeks, for such was the pace set at Shikarpur. Sir Henry's autobiography is a simple, unassuming story of a fine doctor and a true Christian, interlarded with many a humorous anecdote. His description of the terrible earthquake in Quetta is an epic, and rejects the

old story that "Those the Gods love die young," for his own escape from death was in itself a miracle.

Sir Fred Bowerbank's story is cast in quite a different mould, though he too was a religious man. Emigrating to New Zealand at an early age, he became completely absorbed in the New Zealand way of life and passionately devoted to the land of his adoption. Working as a general practitioner for many years, he could not resist the call in 1915 when he joined the New Zealand Expeditionary Force in the First World War. His experiences in this war undoubtedly prepared him for the high posts in medical administration he eventually held in the Second World War, when he became Director of the New Zealand Medical Services. He gives us a most interesting insight into medical practice in New Zealand in the early part of this century. His comments on the political difficulties that arose over the hospitalization and treatment of New Zealand wounded are terse and to the point. A striking feature of the book is the accurate detail of even minor happenings over the years, which could only be the result of a most amazing memory or a meticulously kept diary. It is the story of the very full life of a man generously endowed with the qualities essential in a good doctor also destined to be a good leader of men.

Both these books rank high in an order of merit of good autobiographies. They are well worth reading, not only for the factual material contained in them, but also for the admiration of a job well done which these two long lives, devoted to the service of God and country, induced in the mind of the reader.

J. C. A. DOWSE.

INTRACARDIAC PRESSURE CURVES

Atlas of Intracardiac Pressure Curves. By Otto Bayer and Hans Helmut Wolter. English text by G. R. Graham, M.D. With an introduction by Professor André Cournand. (Pp. 185; illustrated. DM. 68.) Stuttgart: Georg Thieme Verlag. 1959.

The *Atlas of Intracardiac Pressure Curves* is written in German, English, and Spanish. So one really buys three books in one. The authors point out that the study of a large number of curves gives the range of the biological normal. The sources of technical error are fully discussed, but it is pointed out that these should not be large, and certainly should not exceed these natural limits. To begin with there is a short section on theoretical considerations. The registration of the pressures in the different parts of the heart and great vessels is described in detail. The collection of 42 plates at the end illustrates the curves. The description of each appears in three languages. There is a short account of the curves of stenosis and insufficiency of the valves on the right side. The authors warn about the difficulty in interpreting the wedge-pressure curves, and recommend taking several at various places. The effect of shunts on the curves is given. Actually the part in English is only some 12 pages. But there are many illustrations in the German part of 57 pages to which reference is made. The translation is clear and well vetted. The statement is neat and economical. The curves are good and well traced, and show all the usual patterns. The price is really rather high, for one is paying for a good deal that one does not want. There are 87 references and a good index.

TERENCE EAST.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Kompendium der Gesundheitsfürsorge. Einführung in die Lehre Ihrer Prinzipien, Funktionen und Institutionen. By Professor Dr. Erich Schröder. (Pp. 377+vii; illustrated. DM. 39.) Stuttgart: Georg Thieme Verlag. 1959.

Principles of Radiation Dosimetry. By G. N. Whyte. (Pp. 124+vii; illustrated. 56s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall, Ltd. 1959.

Röntgendiagnostik beim Neugeborenen und Säugling. By Dr. Hermann G. Wolf. With a foreword by Professor Dr. K. Kundratitz. (Pp. 317; illustrated. £8 7s. 5d.) Vienna, Bonn, Berne: Wilhelm Maudrich Verlag. 1959.

Brief Course in Organic Chemistry. Second edition. By Lyell C. Behr, Reynold C. Fuson, and Harold R. Snyder. (Pp. 289+viii; illustrated. 46s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall, Ltd. 1959.

That the Patient May Know. An Atlas For Use by the Physician in Explaining to the Patient. By Harry F. Dowling, M.D., Sc.D., Tom Jones, B.F.A., assisted by Virginia Samter. (Pp. 139+xiii; illustrated. 52s. 6d.) London, Philadelphia: W. B. Saunders Company. 1959.

Collected Papers of the Mayo Clinic and the Mayo Foundation. Volume 50, 1958. (Pp. 791+xiii; illustrated. 91s.) Philadelphia, London: W. B. Saunders Company. 1959.

Handbuch der Urologie. Edited by C. E. Alken, V. W. Dix, H. M. Weyrauch, and E. Wildbolz. Vol. IX. Part 2. Inflammation. II: Specific Inflammations. By Einar Ljumggren, R. Campbell Begg, and Ambrose J. King. (Pp. 564+xv; illustrated. DM. 158.) Berlin, Göttingen, Heidelberg: Springer Verlag. 1959.

Diagnostic Biochemistry. Quantitative Distributions of Body Constituents and Their Physiological Interpretation. By Halvor N. Christensen, Ph.D. (Pp. 291+ix. 52s.) New York: Oxford University Press. 1959.

Notes of a Soviet Doctor. By G. S. Pondoev. (Pp. 238+iii. 40s.) New York: Consultants Bureau, Inc. London: Chapman and Hall, Ltd. 1959.

Röntgenanatomie für Ärztliches Hilfspersonal und Röntgentechniker. By Wolfgang Frik, M.D., and Ulrich Goering. (Pp. 82+vi; illustrated. DM. 12.) Stuttgart: Georg Thieme Verlag. 1959.

Psychoanalysis and Psychotherapy. 36 Systems. By Robert A. Harper. (Pp. 182+viii. $1.95.) Englewood Cliffs, N.J.: Prentice-Hall, Inc. 1959.

Die Bewegungsbestrahlung. By Professor Dr. F. Wachsmann, and Professor Dr. G. Barth. Second edition. (Pp. 200+viii; illustrated. DM. 46.) Stuttgart: Georg Thieme Verlag. 1959.

Surgery of the Foot. By Henri L. DuVries, M.D. (Pp. 494; illustrated. 93s. 6d.) London: Henry Kimpton. 1959.

Lehrbuch der Histologie und der Mikroskopischen Anatomie des Menschen. Twenty-eighth edition. Edited by Professor Dr. Kurt Goerttler. (Pp. 560+xvi; illustrated. DM. 36.) Jena: VEB Gustav Fischer Verlag. 1959.

Synopsis of Treatment of Anorectal Diseases. By Stuart T. Ross, M.D., F.A.C.S., F.I.C.S. (Pp. 240; illustrated. 48s. 6d.) London: Henry Kimpton. 1959.

Atti della Società Italiana di Cardiologia XXI Congresso Roma, 28-30 May 1959. Vol. I. ***Prima Relazione.*** (Pp. 234.) Rome: Editi a Cura della Segreteria della Società. 1959.

La Malattie del Collageno in Otorinolaringologia. (Mesenchimopatie Reattive "Regionali"). By Vincenzo Ricci. (Pp. 254+xx; illustrated. L. 3,500.) Pisa: Edizioni "Omnia Medica." 1959.

La Venerologia del Tombolo. By T. Mazzacurati. (Pp. 166. L. 2,000.) Pisa: Edizioni "Omnia Medica." 1959.

Compte-Rendu des Journées Françaises de Pathologie Minière. (Pp. 368; illustrated.) Paris: Charbonnages de France. 1959.

Recent Progress in Hormone Research. Proceedings of the Laurentian Hormone Conference. 1958. Edited by Gregory Pincus. Volume XV. (Pp. 504+xiii; illustrated. $12.50.) New York, London: Academic Press. 1959.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY OCTOBER 3 1959

LIVE POLIOMYELITIS VACCINES

At a conference[1] in Washington, D.C., last June, Professors A. A. Smorodintsev, M. P. Chumakov, and Skovránek described the mass vaccinations with Sabin's live poliovirus vaccines now in progress in the U.S.S.R. and in Czechoslovakia, and the trials which preceded them. Delegates to the recent meeting of the European Association against Poliomyelitis also heard about this important work (see p. 630). The information now available about the Russian and Czechoslovak experience, added to that coming from other countries, calls for a re-examination of the arguments for and against the use of live poliovirus vaccine in Britain.

In preliminary studies in the U.S.S.R. over the past two years, Sabin's vaccines of all three types were fed to groups of children, at first in hundreds, later in thousands. The health of the children was carefully watched and the development of antibodies was measured in the vaccinated groups and in large control groups in contact with them. No ill effects were observed, and the general conclusions of other workers about the production of antibodies, the excretion of virus, and passage of virus from the vaccinated to their contacts were confirmed. Convinced that Sabin's vaccines, whether made in U.S.A. or U.S.S.R., are safe to both the vaccinated and their contacts, Smorodintsev and Chumakov next increased the scale of their operations so that in some areas almost half of the population received vaccine in the spring of this year. It is estimated that by the end of July some 6m. people had been vaccinated in Russia alone. In a parallel programme in Czechoslovakia, Skovránek and his associates had fed vaccine to nearly 150,000 by the end of June; and these schemes are continuing.

From the information made available to the Washington conference, it may be assumed that the manufacture and testing of vaccines and the conduct of the trials have been done with great care and that the results of the mass vaccinations are being watched as closely as is possible with such large numbers. The safety of the vaccine in the mass vaccinations is being judged chiefly on the overall incidence of poliomyelitis in the populations concerned. After several months' experience of giving the vaccine to these enormous numbers, the Russian and Czechoslovak workers were still completely convinced of the safety of the procedure.

Elsewhere, live vaccines made by Lederle Laboratories have been given to hundreds of thousands in Central and South America, and reports of large trials of either Sabin's or the Lederle vaccines have come from Mexico City, Costa Rica, Finland, Poland, and Africa. The important Singapore trial[2] of Sabin's Type II vaccines has already been discussed in these columns.[3] The quality of the surveillance given during all these investigations has probably been very varied, but no untoward results of vaccination have so far been described. The important paper by Dr. Herald Cox and his associates which is published in the opening pages of this issue describes an investigation of the response to trivalent oral poliomyelitis vaccine in 550 volunteers. While the findings do not add much to our knowledge about the safety or efficacy of the vaccine in preventing poliomyelitis, the cumulative value of such scrupulously conducted and relatively small trials is great. Dr. Cox and his colleagues report a satisfactory response to the dose of triple vaccine used, and their paper emphasizes the need for yet more information on questions of dosage and methods of administration.

A strong presumption that live vaccine is safe is created by the numerous very carefully surveyed small trials such as those carried out by Dr. Cox and colleagues, by Dr. Sabin himself, and by others, including recently R. N. Barr and his colleagues in Minnesota[4] and H. M. Gelfand and others in New Orleans.[5] Indeed, those responsible for the mass vaccination programmes have been convinced by all this evidence that live vaccines are safe, in spite of the fact, noted by most of those who have studied the matter, that passage of the vaccine virus through the human intestine restores some of its power to paralyse monkeys. Advocates of live vaccines argue that the increase in neurotropic power so far reported has been trivial: very large doses indeed given by intracerebral inoculation are required to paralyse monkeys. Smorodintsev has found no further increase in paralysing power after up to 10 passages through human intestines and is convinced that the return of virulence is not progressive. An

[1] See *Brit. med. J.*, 1959, **2**, 235.
[2] Hale, J. H., Doraisingham, M., Kanagaratnam, K., Lee, L. H., Leong, K. W., and Monteiro, E. S., ibid., 1959, **1**, 1541.
[3] Ibid., 1959, **1**, 1618.
[4] Barr, R. N., Bauer, H., Kleinman, H., Johnson, E. A., da Silva, M. M., and Kimball, Anne C., *J. Amer. med. Ass.*, 1959, **170**, 893.
[5] Gelfand, H. M., Potash, L., Le Blanc, Dorothy R., and Fox, J. P., ibid., 1959, **170**, 2039.
[6] See *Brit. med. J.*, 1959, **2**, 313.

interesting point in the paper by Dr. Cox and his colleagues is that out of the 550 recipients of the Lederle triple vaccine one experienced transient headache and neck stiffness seven or eight days after ingestion of the vaccine. There seems to be no way of determining whether these symptoms were due to the vaccine virus or not.

Opinion in Britain has so far demanded very strong evidence that the live vaccine cannot, after its release in the community, be a cause of paralytic disease. Such evidence can come only from very careful surveillance of direct and indirect contacts of those vaccinated, continued over a sufficient time, and from increasing knowledge of the factors which control the mutability of virus. For instance, some still consider that the evidence of the Singapore trial as to safety, though strong, is not complete without further information about the surveillance of contacts; and the same may be said of all the other large-scale trials listed above. With the kind of evidence which is now being accumulated in such volume, it may never be possible to be certain in a community well vaccinated with live vaccine, however great the reduction in paralytic poliomyelitis may be, that an individual case of paralysis has not been caused by the vaccine: on present knowledge it would be equally difficult to prove the vaccine responsible for an individual case of paralysis.

This argument against the vaccine is cogent if its efficiency in affording protection is unknown, but would become academic if the vaccine were known to be highly effective. We do not yet know that the live vaccine is more effective than the formol-inactivated vaccines in use in this country. The low incidence of poliomyelitis in the United Kingdom in the present season so far might be held to reflect the efficacy of the Ministry of Health's vaccination campaign. However, the experience of the U.S.A. and Canada is not so good this year as last year,[6] and it seems clear that the inactivated vaccine as now made and used does not give complete protection, and cannot be expected to eradicate poliomyelitis. Formolized vaccines have the further disadvantages that they are expensive to make and to administer, and probably, as used, do not give a very durable immunity unless vaccination is repeated.

If the Russian and Czechoslovak trials in the coming months fulfil their early promise, and are associated with a very substantial fall in the incidence of poliomyelitis, the relative merits of live vaccines and formolized vaccine for use in this country will call for careful appraisal; and it may well be that if a parent asks, "Which gives my child the best chance of avoiding poliomyelitis—to be vaccinated with live or with formolized vaccine, or not to be vaccinated at all?" the correct answer in six months' or a year's time should be, "To be vaccinated with live vaccine." No one yet knows what the real answer to such a question will be, but the events of the past six months have substantially increased confidence in the safety of live vaccine, and hinted that it may prove very effective.

Meanwhile, it is important that those in Britain who are concerned with this problem should enlarge their experience of handling, making, testing, and generally studying live poliovirus vaccines. Most will agree that the safety of live vaccines has now been sufficiently established to justify more extended investigations of their effect on those receiving them and of the mutability of the virus. Much has yet to be learned about methods of administration, dosage, the effect of earlier vaccination with "killed" vaccine, and, especially, about the characteristics and behaviour of vaccine viruses after their passage through human intestines. Their efficacy in preventing, possibly in eliminating, poliomyelitis can be judged only on the overall effect of their use on a mass scale—that is, on nearly the whole of a population. They are now being employed on such a scale in several countries.

LEUKAEMIA AND RADIATION

Mortality from leukaemia during infancy and childhood shows a distinctive pattern. The death rate rises from the first year of life to reach a peak between the ages of 3 and 4 years, and thereafter steadily declines. The peak is distinct, and during the period 1955–7, the latest three years for which data are available,[1] the death rate in England and Wales between the ages of 4 and 5 years was as high as 66 deaths per million children of both sexes in this age group.

Lately there has been considerable interest in the possibility that exposure to radiation in prenatal life may increase the risk of both childhood leukaemia and other forms of cancer. In 1956 Dr. Alice Stewart and her colleagues, of Oxford, published a report drawing attention to this possibility,[2] and in a more extended paper[3] the same authors claimed that

[1] Registrar-General, *Statistical Reviews of England and Wales*, Part I, *Tables, Medical, 1955–57*, H.M.S.O., London.
[2] Stewart, A., Webb, J., Giles, D., and Hewitt, D., *Lancet*, 1956, **2**, 447.
[3] —— —— and Hewitt, D., *Brit. med. J.*, 1958, **1**, 1495.
[4] Polhemus, D. W., and Koch, R., *Pediatrics*, 1959, **23**, 453.
[5] MacMahon, B., paper presented to American Public Health Association, 1958.
[6] Court-Brown, W. M., and Doll, R., *Lancet*, 1957, **1**, 97.
[7] —— —— *Spec. Rep. Ser. med. Res. Coun.* (*Lond.*), No. 295, H.M.S.O., London, 1957.
[8] Lejeune, J., Gauthier, M., and Turpin, R., *C.R. Acad. Sci.* (*Paris*), 1959, **248**, 602.
[9] Jacobs, P. A., Baikie, A. G., Court-Brown, W. M., and Strong, J. A., *Lancet*, 1959, **1**, 710.
[10] Muller, H. J., in *Radiation Biology*, 1954, **1**, 358.

prenatal exposure approximately doubled the chance of a child dying from leukaemia or cancer before the age of 10 years. Since 1956 other workers have published reports on the same topic, but their reports have been contradictory. The latest of these is one by D. W. Polhemus and R. Koch,[4] who failed to find a significant association between childhood leukaemia and prenatal irradiation. However, in this study satisfactory data were obtained for only 251 out of the 317 leukaemic children who formed the basis of the inquiry; as full radiation histories of the other 66 children could not be elicited, too much reliance cannot be placed on the results.

All the surveys that have been reported have been retrospective, and in such circumstances the choice of suitable control groups can be very difficult. Thus the mothers of dead children might have a sharper recollection of past events than mothers who have not suffered a similar bereavement. Such a possibility is suggested by the findings of the Oxford survey, in which the mothers of the leukaemic children reported that they had had *x*-ray exposure to the abdomen more frequently before marriage, as well as during the relevant pregnancy, than did the control mothers. When *x*-ray examinations of other sites were considered, the mothers of the leukaemic children reported having had such exposures more frequently before marriage, between marriage and the relevant pregnancy, and also during the relevant pregnancy. Furthermore, the same mothers reported having had more illnesses during pregnancy than the mothers of control children. This does not controvert the fact that exposure of the abdomen to *x* rays during the relevant pregnancy was reported most often by the mothers of leukaemic children, but it does suggest that the control mothers were under-reporting their radiation histories. It is therefore desirable, despite the difficulties, to organize retrospective surveys that are not dependent on the memory of the mother for details of her exposure to *x* rays. B. MacMahon[5] has carried out such a survey in New York which so far has shown no evidence of an increased mortality from leukaemia among children exposed *in utero*, though there was some evidence that their mortality from other forms of cancer was higher than might have been expected. The author admits, however, that the numbers in his survey are as yet too small for any firm conclusions to be drawn.

Such arguments offer little comfort to the obstetrician and the radiologist. What they need information on is, first, the relation between low doses of radiation and the incidence of leukaemia, and, secondly, the radiosensitivity of the foetus in comparison with that of the child and the adult. It has been estimated, on the basis of findings among cases of ankylosing spondylitis, that about 20,000,000 adults would have to be studied for 10 years in order to detect the leukaemogenic effects of a mean marrow dose of 1 rad in excess of that received from natural background radiation.[6] Since relatively small doses reach the foetus in antenatal radiography, it is evidently impracticable to obtain, by epidemiological methods, direct evidence on the leukaemogenic risk to the foetus unless the sensitivity of the foetus is much greater than that of the child or adult. If eventually a negative result accrues from the various surveys that have been and are being carried out, it will show only that the foetal sensitivity is not so great as was thought, not that no risk is present.

The data of Dr. Stewart and her collaborators give a lead on the problem of sensitivity, as they suggest that the foetus may be much more sensitive during the first half than during the second half of pregnancy. This is in keeping with other knowledge indicating the harmful effects of exposure to radiation when the foundations of the main organs are being laid—for example, the finding of microcephalic children irradiated at an early stage of foetal life in Hiroshima. There are good grounds, therefore, for avoiding all exposure to the foetus during the first half of pregnancy unless the need is imperative.

But what of the second half of pregnancy? It is suggested that at the very least the same caution should be adopted towards foetal exposure as ought to be adopted towards exposure of the child and the adult. It has been postulated that leukaemia may result from damage to the genetic mechanism of a cell,[7] and this can be caused by low doses of radiation. Recent knowledge serves to substantiate such a hypothesis, for the demonstration that mongols possess an additional chromosome may well be relevant to their predisposition towards leukaemia.[8,9] The additional chromosome is probably due to non-disjunction of chromosomes either during parental gametogenesis or possibly at an early stage of cleavage of the fertilized ovum. The consequence would appear to be that marrow cells with a genetic mechanism carrying such an abnormality are unusually prone to the development of leukaemia. H. J. Muller[10] has drawn attention to the fact that exposure to radiation increases the frequency of non-disjunction both at meiotic and at mitotic division. These, therefore, are cogent reasons for keeping foetal exposure during the second half of pregnancy to the necessary minimum.

HEALTH SERVICE POLICY

The General Election on October 8 is the fourth since the National Health Service came into being in 1948. A number of medical men and women are standing as candidates. We have invited them to give, in a few words, their views on reform of the N.H.S. The replies which we received are published in this week's *Supplement*, together with biographical details of each candidate.

The doctors standing for election are doing so as political aspirants whose duty, if elected, will be to their constituents. Nevertheless, their colleagues outside Parliament will be especially interested to know what they are thinking about the N.H.S. Of the twenty-one now at the hustings some will soon be able to write on House of Commons notepaper. So we may take this opportunity to remind them of a few of the points in present B.M.A. policy.

The B.M.A. has "demanded" that not less than £750m. shall be spent on new hospital buildings in the next ten years, and Council has been instructed to give the report on hospital building by Mr. Lawrence Abel and Mr. Walpole Lewin[1] "the widest possible publicity" among members of all political parties. The Representative Body has also pressed for increases in the establishment of consultants wherever there is need. Furthermore, in plans for new hospitals and alterations to old ones provision should be made for general-practitioner beds, and beds for general practitioners are "a fundamental requirement" in a maternity service. The B.M.A. has consistently advocated that private patients should be allowed their drugs through the N.H.S., and this principle was reaffirmed this year. Also reaffirmed was the policy "that the shilling charge on prescriptions be abolished." The Association has always favoured the preservation of private practice, and in line with this was a resolution by the Representative Body in Edinburgh which instructed Council to press for moderately priced pay-beds even if amending legislation is needed. The R.B. deplored the recent "considerable rise" in the cost of private beds as much as it deplored the inability at present of private patients to have their drugs free.

Measures for improving the public health are in the forefront of B.M.A. policy. In 1958 the Association asked the Government to inquire into the dangers of the continued disposal of sewage into the sea and rivers, and it also urged that the provisions of the Clean Air Act should be carried out expeditiously. The low level of immunity against smallpox is another matter of concern, and the Association wants a campaign to correct this. The Representative Body wishes to see better facilities for the care of the chronic sick, particularly the physically handicapped, and the aged, and also advocates the establishment of day hospitals and evening clinics for the mentally sick.

Since the status and wellbeing of the profession are now so much at the mercy of politicians it is not unreasonable to remind them that the remuneration of doctors in the N.H.S. has remained unchanged, apart from two small interim adjustments, since 1951. The Royal Commission's report is now awaited, and all doctors will be united in an expectation that whatever political party is returned to power it will make it its business to remedy an injustice which has been outstanding too long.

[1] *Brit. med. J., Supp.*, 1959, **1**, 109.

POST-OPERATIVE MYOCARDIAL INFARCTION

Mortality from acute myocardial infarction is high during the first week, and deaths are twice as common when a myocardial infarct occurs during or immediately after a surgical operation. Fortunately, it is not a common complication of surgical operations. An investigation of 20,000 operations revealed only 15 authentic cases (0.075%)[1] and, more recently, a study of 21,000 patients showed only 35 (0.17%) with electrocardiographic or necropsy evidence of myocardial infarction.[2] Nevertheless, in 1,011 cases of acute myocardial infarct 85 (8%) were within one month of a surgical operation.[3,4]

Patients most likely to have a myocardial infarct are those who have shown clinical features of coronary disease before the operation. When patients have angina, hypertension, or congestive failure, or have a history of myocardial infarct, then particular care should be taken to prevent a fall in blood pressure, tachycardia, or haemorrhage. The greatest danger to these patients is prolonged shock[5] or serious hypotension, which can reduce the coronary blood flow. Older patients are often more sensitive to anaesthetics, and bad anaesthesia can lead to respiratory depression with anoxia and hypotension or tachycardia with a decrease in coronary blood flow. The type of inhalation anaesthetic is not of great consequence, but spinal anaesthesia is more hazardous than others to patients with coronary disease. A recent analysis[6] of multiple-lead electrocardiograms has shown that myocardial ischaemia commonly develops during hypotensive anaesthesia. Moreover, K. T. Lee and R. M.

[1] Wróblewski, F., and La Due, J. S., *J. Amer. med. Ass.*, 1952, **150**, 1212.
[2] Feruglio, G., Beliet, S., and Stone, H., *Arch. intern. Med.*, 1958, **102**, 345.
[3] Lee, K. T., and O'Neal, R. M., *Arch. Surg. (Chicago)*, 1956, **72**, 622.
[4] Master, A. M., Dack, S., and Jaffe, H. L., *J. Amer. med. Ass.*, 1938, **110**, 1415.
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[7] Baker, H. W., Grismer, J. T., and Wise, R. A. *Arch. Surg. (Chicago)*, 1955, **70**, 739.
[8] Jacobs, T. P., *Ann. intern. Med.*, 1951, **34**, 114.
[9] Paton, B. C., *Amer. J. Med.*, 1957, **23**, 761.
[10] Menhard, O. J., and Hurxthal, L. M., *Surg. Clin. N. Amer.*, 1931, **11**, 335.

O'Neal[3] have reported that 30% of their 50 cases of post-operative myocardial infarction were given a spinal anaesthetic, and emphasized that undue fluctuation of the blood pressure during anaesthesia should be avoided. Local infiltration and regional nerve block are seldom followed by myocardial infarction,[7] and are particularly suitable, therefore, for patients who had a myocardial infarct less than three months before the operation.

Most post-operative myocardial infarcts happen after major operations and within the first three days—many on the day of operation. The diagnosis is not easy. The patient is often under heavy sedation or still partly anaesthetized. Severe praecordial pain is uncommon[2 4 8] and post-operative myocardial infarction is often painless. Persistent hypotension and post-operative collapse are the commonest initial signs and arose in 9 out of 15 cases reported by A. M. Master and colleagues.[4] Orthopnoea and a persistent tachycardia are often present, and the development of an abnormal rhythm should be regarded with suspicion. Pulmonary oedema occurs occasionally, and the unexpected development of congestive heart failure after a surgical operation should suggest the possibility of myocardial infarction.

But this condition is not the only cause of post-operative hypotension, breathlessness, praecordial pain, and collapse, and often such a diagnosis is not subsequently substantiated by an electrocardiogram or by necropsy.[8] Pulmonary collapse and pulmonary infarction are probably the two post-operative complications most commonly diagnosed as acute myocardial infarction. Others include traumatic shock, haemorrhage, meteorism, paralytic ileus, and post-operative acute pancreatitis.

A recent report[9] has shown the importance of electrocardiography in the accurate diagnosis of myocardial infarction: even in a large teaching hospital, a clinical diagnosis of this disorder unsupported by electrocardiographic confirmation may be wrong in as many as 45% of patients. So long ago as 1931 O. J. Menhard and L. M. Hurxthal[10] advocated the more frequent use of electrocardiography in the investigation of unusual post-operative syndromes. This is wise advice. A standard 12-lead electrocardiogram is the most precise way of excluding a recent myocardial infarct as a cause of post-operative collapse. It will seldom be negative if a myocardial infarct is present, and two negative electrocardiograms within 24 hours usually exclude the possibility. Transaminase levels are likely to be raised in consequence of the surgical damage to tissues and are therefore of little or no value in indicating the presence of myocardial damage.

Individual prognosis depends on many factors, including the severity of the myocardial infarct, the development of cardiac failure, the presence of anaemia, and the speed with which efficient treatment can be instituted. Once the diagnosis has been established by an electrocardiogram the need for the intravenous administration of digitalis must be considered. When the cardiac output has been reduced by acute myocardial infarction the risk of pulmonary oedema or congestive heart failure is considerable in patients who require intravenous fluids. It may be sufficient to restrict the amount of fluid given, but it is likely that the prompt intravenous administration of digoxin will be neccessary. Full treatment with digitalis is often essential for the adequate management of the hypotension and cardiac failure which often follow acute myocardial infarction, and it is likely to be specially beneficial to the patient who develops these disorders when the infarction is in the post-operative period. The continuous administration of oxygen will be particularly beneficial when much blood has been lost. Anticoagulants are seldom contraindicated,[1] but heparin should not be given unless the dose is precisely controlled by serial clotting times; arbitrary uncontrolled doses of heparin can be dangerous in the post-operative period. The slower-acting oral anticoagulants, phenindione or ethylbiscoumacetate, should be given in modified doses to most patients with post-operative myocardial infarction in order to keep the prothrombin time not more than twice the control value or prothrombin activity not less than 25%. Patients with liver disease, jaundice, or an active peptic ulcer should not receive anticoagulants.

It is likely that the risk of post-operative myocardial infarction is least when particular attention is given to the pre-operative management of cardiac failure, arrhythmias, anaemia, or electrolyte imbalance—especially for the patient who has clinical features of coronary disease. Then it is worth taking special care to avoid hypotension and to reduce to a minimum damage to tissue, loss of blood, and anoxia.

SYNNEMATIN B IN TYPHOID FEVER

The treatment of typhoid fever with an antibiotic called synnematin B has been reported several times. This substance is identical with cephalosporin N, and is a form of penicillin.[1] N. D. Henderson and his colleagues[2] described the course of typhoid fever which a 37-year-old woman contracted during a family visit to Mexico. Penicillin and another unidentified antibiotic had been given before the diagnosis was made, and chloramphenicol[3] was given after *Salmonella typhi* had been recovered from both faeces and blood, but her condition deteriorated and she became semi-comatose, with high fever and "bleeding grossly from the intestine." She was then given synnematin B intramuscularly at intervals of four hours, the total daily dose amounting to 80,000 units per kg. body weight. Within two days she improved, though fever abated more slowly; blood cultures became negative and stool cultures only intermittently positive. Complete recovery followed, to be interrupted only by the rupture of an ovarian cyst, producing a peritonitis from which *Salm. typhi* was cultivated. Stool cultures were negative at that time and on 18 subsequent occasions. Her son, who accompanied her to Mexico, and her father-in-law also had milder attacks of typhoid fever, which responded to chloramphenicol. A series of cases of

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[2] Henderson, N. D., Garlock, F. C., and Olson, B. H., *J. Amer. med. Ass.*, 1959, **169**, 1991.
[3] Benavides, V. L., Olson, B. H., Varela, G., and Holt, S. H., ibid., 1955, **157**, 989.
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[5] *Brit. med. J.*, 1959, **1**, 701.

typhoid fever were treated with synnematin B in Mexico City by V. L. Benavides and his colleagues[3] four years ago with good results.

Penicillin itself in very large doses has been successful in the treatment of this disease.[4] The advantage of the penicillins over chloramphenicol is that they are bactericidal. Thus the typhoid bacillus is eliminated instead of being merely suppressed, and both relapses and the persistence of a carrier state which are apt to follow treatment with chloramphenicol should be much less common if treatment with synnematin B replaced it. There are doubtless many workers in different parts of the world who would like to test the truth of this for themselves, but have not been able to do so because the antibiotic is unobtainable. This is believed to be because the adequate purification of synnematin B is not an economically feasible process. The present authors do not state the source of their supplies or the degree of purity of the product; "no evidence of toxicity" was observed and local reactions to injection are not mentioned. It is unusual for the name of the manufacturers of such a product as this to be omitted from the paper, and the omission may mean that further requests for it are not desired. At a time when fresh efforts are being made to obtain new penicillins with other therapeutic properties[5] it seems a pity that a known penicillin with at least one important therapeutic use should be neglected simply because of production difficulties.

QUESTIONS ON THE MIND

Since the beginning of this century scientific psychologists have been trying to eliminate that unreliable chap, the clinical psychiatrist. Sometimes they try to "objectify" diagnosis or prognosis, but their main efforts have been directed to the "measurement" of intelligence and personality. Intelligence testing is, of course, well established. Personality testing has been approached in several ways, the commonest being projection tests, which seek to explore the "deeper" aspects of personality, and questionaries.

The specious simplicity of questionaries has led to a great burgeoning of them. To their number Professor H. J. Eysenck[1] has added another which has certain advantages. For one thing there are only 48 questions in his Maudsley Personality Inventory compared with up to ten times as many in other lists. Moreover, an almost equally reliable and valid estimate can be made of neuroticism or introversion by using only six of the questions. This reduction is possible because of overlap between the questions. Compare, for example,

16. Is it difficult to "lose yourself" even at a lively party?

38. Can you usually let yourself go and have a hilariously good time at a gay party?

Or again:

2. Do you sometimes feel happy, sometimes depressed, without any apparent reason?

7. Are you sometimes bubbling over with energy and sometimes very sluggish?

10. Are you inclined to be moody?

11. Do you have frequent ups and downs in mood, either with or without apparent cause?

17. Do you ever feel "just miserable" for no good reason at all?

35. Have you often felt listless and tired for no good reason?

Much work must have gone into the validation of these questions: their similarity to those used by psychiatrists says much for the latter's acumen.

The correlations of the M.P.I. with other scales reveals some interesting facts. The M.P.I. correlates 0.34 and 0.53 with the A and B forms of the Cattell neuroticism scale,[2] and 0.65 and 0.67 with the corresponding introversion scale. This is apparently regarded as pretty good. In fact it would seem that either these scales are not measuring the same factors or they are not measuring them very accurately. It would be two poor clinicians whose findings did not correlate more highly.

Personality questionaries have three disadvantages. Deceit is easy. For example, as personality inventories have become important in personnel selection, so there have developed guides to how they should be answered in order to satisfy a prospective employer. William H. Whyte[3] advises that to settle on the most beneficial answer to any question, you must repeat to yourself:

(a) I loved my father and my mother, but my father a little bit more.
(b) I like things pretty well the way they are.
(c) I never worry much about anything.
(d) I don't care for books or music much.
(e) I love my wife and children.
(f) I don't let them get in the way of company work.

Deliberate deceit is probably only one of the lesser disadvantages of questionaries and one to which Professor Eysenck is alive. A greater disadvantage is that questions are sometimes asked which are impossible to answer sensibly. Consider the following paraphrased from the Bernreuter Personality Inventory:[4]

A woman and child are at the window of a house which is on fire. What would you do?
(a) Call the fire brigade.
(b) Rush into the house.
(c) Fetch a ladder.
(d) Try and catch the baby.

What you should do depends on how big the fire is, whether they are on the first floor or the third, whether there is a ladder handy, how far the house is from the fire brigade, and so on. Candidates having to play this stupid game are forced to make a decision without being in possession of the facts. Understandably, intelligent people find this difficult. The third drawback is perhaps the most serious. It is that even an apparently simple question calls for a degree of self-knowledge which not everyone possesses. "Is it difficult to 'lose yourself' even at a lively party?" "Well, sometimes it is and sometimes it isn't. It depends whether I'm having an up and down with or without apparent cause. . . ." Owing to these disadvantages, the psychologist must be an experienced person if the results of objective questionaries are to be reliable and valid. There has therefore arisen that contradiction in terms, the clinical psychologist.

[1] Eysenck, H. J., *Manual of the Maudsley Personality Inventory*, 1959, London.
[2] Cattell, R. B., *J. cons. Psychol.*, 1956, **20**, 411.
[3] Whyte, W. H., *The Organization Man*, 1957, London.
[4] Bernreuter, R. G., *The Bernreuter Personality Inventory*, copyright 1935 by the Board of Trustees of Leland Stanford Junior University.

SYMPOSIUM ON POLIOMYELITIS

[From a Special Correspondent]

The sixth symposium of the European Association against Poliomyelitis was held at Munich—an ideal conference centre—early this month. It was attended by nearly 500 men and women from twenty-one European countries and from the U.S.A., Turkey, and the Belgian Congo.

Live Polio Vaccine

The highlight of the meeting was the discussion about vaccination with attenuated live virus by mouth. Dr. A. B. Sabin (U.S.A.) was at the symposium as champion of this method. Advantages claimed for this type of vaccine are that it is easier to make and to administer, that it spreads through the community and therefore immunizes more than the individual receiving it, and that it immunizes the alimentary tract so that virulent poliomyelitis virus cannot multiply there and the subject cannot become a carrier. But two questions must be answered before attenuated live vaccine can be accepted: Is it safe? Is it effective? Armchair arguments about the safety of the live vaccine are, as Dr. Sabin stressed, no longer relevant, for field trials on an enormous scale have now taken place. Attenuated live vaccine of type II was given by Professor J. H. Hale and his colleagues to about 200,000 children in Singapore during an epidemic of type I poliomyelitis, and spread rapidly through the community without any signs of recovering its virulence.* In Czechoslovakia, as Dr. Skovranek told the symposium, live vaccine of type I, and in many cases of types III and II also, was given to nearly 150,000 children and proved perfectly safe. Moreover, antibodies were found in a very high percentage of vaccinated individuals, including those who had previously failed to produce antibodies when vaccinated with killed vaccine. The Russians were unable to send delegates to the symposium, but submitted a report describing the vaccination of 6,250,000 people with live vaccine made from Sabin's attenuated virus of types I, II, and III. They had observed no untoward effects, had found a good antibody response, and had accepted the vaccine as a safe and effective preparation. The official conclusions of the symposium were guarded, but many of those who attended it felt that the live vaccine was likely to be widely adopted in the near future.

Diagnosis and Complications

Another virological problem that was discussed was the diagnosis of poliomyelitis from other virus diseases that can simulate it, such as infection with the Coxsackie and E.C.H.O. viruses. Drs. Von Magnus and A. Godtfredsen (Denmark) demonstrated the dangers of relying on antibody levels in the serum in this connexion, and concluded that for some time to come we shall have to rely on the rather cumbersome isolation and identification of the virus itself. Unfortunately facilities for this in Britain are at present limited.

Drs. Ritchie Russell and J. M. K. Spalding (United Kingdom) referred to observations of physiological interest made on patients with complete or very severe respiratory paralysis† and discussed their implications for artificial respiration in clinical practice. The incidence of renal calculi in poliomyelitis was considered by Drs. Falck Larsen and Philip (Denmark) and by Dr. W. H. Kelleher (United Kingdom). Drs. Larsen and Philip had followed up cases from the big epidemic in Copenhagen in 1952, and showed that infection of the urinary tract was an important predisposing cause, and that urolithiasis was especially likely to occur in adults, in males, and in those with severe paralysis.

* Hale, J. H., Doraisingham, M., Kanagaratnam, K., Leong, K. W., and Monteiro, E. S., *Brit. med. J.*, 1959, **1**, 1541.

† Opie, L. H., Spalding, J. M. K., and Stott, F. D., *Lancet*, 1959, **1**, 545.

SOCIETY FOR SOCIAL MEDICINE

The third annual meeting of the Society for Social Medicine took place in Dundee at the Medical School of the University of St. Andrews from September 17 to 19. The meeting, which was attended by some 70 members and their guests, was largely devoted to scientific communications. These were presented under four main headings; Industry; Hospital Patients; Child Health; and General. Below are summaries of some of the papers.

Dust Disease

The early part of the session on industry was occupied by a symposium presented by the host department on "Dust Diseases in Dundee." Professor A. Mair and Dr. W. A. Wilson reported on the incidence of chronic respiratory disease amongst workers in the jute industry. They found no evidence of excess of chronic bronchitis among jute workers or of any specific disease associated with jute as byssinosis is associated with cotton. They did find evidence of byssinosis, however, among the flax workers. Dr. R. S. F. Schilling and Dr. C. B. McKerrow described investigations into the importance of the size of the dust particles in byssinosis in cotton workers. Dr. Schilling's epidemiological evidence indicated that symptoms were associated with a medium size of particle, while Dr. McKerrow's studies of ventilatory function incriminated the smallest particles. Discussion centred around this apparent conflict, which, it was thought, might be explained by the fact that symptoms did not necessarily parallel the severity of the pulmonary damage.

In this section also Dr. C. R. Lowe described the results of an inquiry which had demonstrated an association between cigarette-smoking and both absenteeism and industrial injury in a large Birmingham factory. The association with medical absenteeism was most marked in the elderly workers, and the association with injury most marked in the younger group.

Hospital Patients

Dr. Jean Mackintosh presented part of the results of an inquiry into the needs of patients admitted to hospital. The proportion of admissions classified as avoidable varied markedly with the observer. Whereas few admissions were regarded as avoidable by a hospital consultant, a general practitioner found a high proportion of avoidable admissions in similar hospital patients.

Dr. R. Sutherland reviewed the literature on the relationship between delay in seeking treatment for breast cancer and ultimate survival rates. Short delay was associated with better survival than slightly longer delay, but long delay was associated with the most favourable survival. Dr. Sutherland's conclusion was that, since short-delay patients experienced more favourable survival than all cases combined, the data could be said to support the view that early treatment favours survival. Dr. R. Weir discussed hospital admissions for perforated duodenal ulcer. There had been a secular rise in incidence from 1946 to 1955, but since then the number of admissions had fallen almost to the level of 1946. One of the more striking findings was the trend for perforations to be more common in the lower social classes. There was an excess of cases among single men aged 40 to 50 years.

Other Subjects

Dr. Josephine Webb, using data from the survey of childhood malignancies, said there was a significant excess of histories of antibiotic treatment in children subsequently dying from non-lymphatic leukaemia, but an excess of histories of sulphonamide administration in children dying from lymphatic leukaemia. Dr. E. G. Knox discussed the incidence of congenital oesophageal atresia, and Mrs. M. Jefferys analysed factors determining the acceptance or rejection of vaccination against poliomyelitis. Dr. Lilli

STEIN emphasized the need for revising current methods of occupational and socio-economic classification. Dr. R. M. ACHESON and Professor W. J. JESSOP had studied the serum proteins in a group of men retired from a large brewery in Dublin. Albumin levels showed a slight relation to meat intake, and beta-globulin levels were raised in men who drank more than 12 pints (6.8 litres) of stout a day. No association was found between albumin levels and proteinuria, but proteinuric patients showed a raised gamma-globulin.

New Appliances

A NEW BIOPSY CANNULA

Dr. STANLEY WEINER, of the Department of Pathology, University of Melbourne, Melbourne, Australia, writes:

The choice of an apparatus for the now indispensable technique of needle biopsy depends largely on the organ and the route of investigation, and obviously no universal tool is conceivable. In electron microscopy we were repeatedly inconvenienced by failure to obtain consistently suitable material. This prompted us to scrutinize the efficiency of biopsy equipment in use.

Apparently none of the available biopsy needles offers a reasonable compromise of safety, speed, and consistency in routine application. A critical review of existing types of apparatus, outlined below, has led to the development of a new cannula which shows a well-balanced variety of practical values. It is believed that the main obstacle to consistent results is of a technical nature.

The dangers associated with the liver biopsy alone, roughly indicated by the mortality of 0.12–0.17% (Terry, 1952; Zamcheck and Sidman, 1953), cannot be counteracted by a mere increase of the list of contraindications to biopsy, as this would defeat the purpose. On the contrary, a safe procedure would enable the clinician to widen the scope of indications and give the necessary confidence to a less experienced investigator usually responsible for a higher share of failures.

Functional Principles of Biopsy Apparatus

Biopsy tools in use can be divided into four principal groups: (1) aspiration needles, (2) cutting trocars, (3) forceps types, and (4) double cannulae.

1. Small-gauge needles, as used since the nineteenth century (mainly for smear preparations), when the novelty of approach called for a safe procedure, were not satisfactory; but they must be given due credit for clearing the way for many ingenious devices to come. The application of larger-bore needles was the next logical step. The indispensable suction arrangement, however, often caused a complete occlusion of the needle-tip, and this remained the greatest disadvantage of the technique, which is now seldom used.

2. The increase in the diameter of the instrument paved the way for the trocars. Various combinations of a stylet with a rotating cutting cannula were introduced. The edge of the cannula was corrugated (Iversen and Roholm, 1939) or deeply serrated (Franseen, 1941). In our opinion, any rotated cannula must produce tearing effects unless the cutting edge is perfectly smooth, as used in high-speed rotation methods. If by chance the cylinder of tissue was neatly cut, it still had to be removed by suction, which so often caused the obstruction of the tip. The passage of air and fluid was slightly improved by a spiral grooving of the stylet introduced by Gillman and Gillman (1945) in their ingenious though elaborate apparatus with pre-set suction; but the problem of the detachment of the tissue cylinder and its removal remained unsolved. High-speed rotation has been tested with good results, especially on hard tissues, since its introduction by Kirschner (1935). The latest apparatus by Berci (1958), comprising a pneumatic drill with pre-set depth of penetration, is undoubtedly very efficient, although bulky and expensive and therefore beyond the reach of the smaller hospital units.

3. The gradual increase in the popularity, and the effective evaluation of deep biopsies, have caused a change in the cautious attitude towards the methods. Safety was partly sacrificed in order to obtain the material each time a biopsy was performed. Consequently the Silverman (1938) split needle quickly became popular. The tissue is removed by the unfailing squeezing action of two cutting-spreading prongs. There is a danger of grasping too much and too firmly (for example, a vessel or a duct) and of causing additional trauma by an uncontrolled movement of the retaining cannula relative to the split needle. To control these movements several guards and modifications were evolved (Tripoli and Fader, 1941; Hoffbauer, 1947; Voegtlin, 1948; Sborov, 1950; Nelson, 1952). The result of these attempts was the modified needle introduced by Silverman in 1954. Characteristically, such minor improvements were often accompanied by claims of absolute efficacy, seldom verified by subsequent users.

4. The double cannulae had shown some promise when Roth and Turkel (1944) modified the Turkel sternal biopsy punch for application to prostatic biopsies. For the actual biopsy, the obturator is exchanged for an inner cannula with serrated cutting edge. There is no provision for detachment of tissue. A logical attempt to cut off the fragment of tissue was shown most recently in the pleural-biopsy punch of Abrams (1958). A notch on the side of an introduced cannula is pushed sidewards towards the pleura at the end of aspiration of pleural effusion. An internal cutting cylinder is then advanced in spiral fashion and any tissue that may protrude into the lumen is sheared off. The size of the biopsy specimen is limited and the necessary side motion of the needle makes it dangerous for parenchymatous organs.

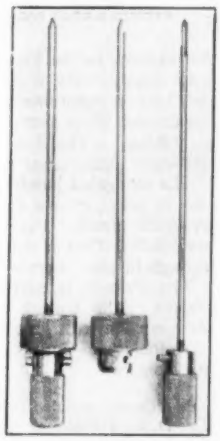

FIG. 1.—The cannula in closed position (left) and dismantled (centre and right).

The New Cannula

Considering the disadvantages outlined above (the Berci and the Abrams apparatus had not been published at that time) we arrived at the conclusion that there was a need for a tool which would consistently give a representative controllable length of tissue and which would cut down the risks of the operation at the same time. Such apparatus had to be simple, fast (that is, no manipulation of accessories while the needle is being inserted), safe in penetration (determined largely by the shape of the tip), and requiring no special experience.

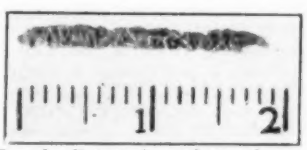

FIG. 2.—Extracted specimen photographed against a millimetre scale.

A prototype was at first (1957) declared by instrument makers to be too difficult to produce. Finally an instrument to our specifications was made* in stainless-steel tubing with chromed brass handles in the shape shown in Fig. 1. The internal cannula is of I.D. 0.062 in. (1.47 mm.), O.D. 0.078 in. (1.98 mm.), and one-half of its rounded pointed end is cut out to the length of approximately ½ in. (12.7 mm.). A snugly fitting external cannula (I.D. 0.08 in. (2.03 mm.), O.D. 0.096

*C. Alger and Sons, Pty. Ltd., instrument makers, 25, Market Lane, Melbourne, C.1.

in. (2.44 mm.)) has a similar shorter cut with a forward inclined cutting tooth at its base. In the closed position the needle looks and acts like a stylet which is being introduced into the organ. The inner needle is turned by 180 degrees to a stop, and in this "open" position it is thrust into the tissue to the desired depth, which can be limited by a stop of the type used on pneumothorax needles. During this movement a uniform cylinder of tissue enters the cannula, while tissue elements which meet the point of the needle on the rounded side are deflected. The cannula opening is then closed—that is, the tissue-cylinder is safely cut off at its base. The actual operation of cutting, closing, and removing can be accomplished in less than two seconds at the first attempt. The specimen (Fig. 2) is not compressed, torn, or rotated, and is expelled from the cannula in "open" position by a steady stream of fixative applied by a syringe which can be inserted into the opening provided in the inner handle.

Liver specimens up to 1 in. (2.5 cm.) long were obtained without artifacts. Examination of the needle track at necropsy (where the individual had died of a condition unrelated to the puncture) has shown no tear (Fig. 3), and

FIG. 3.—Photograph showing a liver capsule scar (left) and cannula's track (centre and right) 10 days after biopsy.

the opening in the liver capsule was much smaller than the track itself, owing to the smooth curving of the closed tip. As there is no removal of a stylet, no rotation, and no attachment of a suction syringe, the risk of a lateral tear is minimal. The action is simple and fast, which is of particular importance in the intercostal approach.

The elongated handle gives a good control. The cannula can be made to any specified diameter within the range of available tubing. The latter can be very thin because of the reinforcing effect of the double wall. The tool is thus sturdy enough to give years of service.

The cannula is particularly suitable for parenchymatous organs. The cutting tooth, on the other hand, can be sharpened to suit special requirements.

Autoclaving and storing are done in the "closed" position.

My thanks are due to Dr. J. F. Funder, Dr. I. Epstein, and Dr. D. C. Forster, of the Prince Henry's Hospital, Melbourne, for their willing assistance in the clinical evaluation of the new instrument.

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To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Mysoline (Imperial Chemical Industries).—Primidone is chemically 5-phenyl-5-ethylhexahydropyrimidine-6-dione, and is structurally related to phenobarbitone. It is readily absorbed when given by mouth, and is excreted in the urine, about half unchanged and half metabolized.

Therapy.—This drug is a potent anticonvulsant with a specific effect on the convulsions of grand-mal epilepsy. Despite some claims, it is not of benefit in cases of pure petit mal, and is of limited use in controlling focal fits.

It is wise to begin treatment with a very small dose—one-quarter of a 0.25-g. tablet on the first day. The dosage is then rapidly increased until one 0.25-g. tablet is given three or more times a day, this dosage being attained within a week.

Owing to the relatively high cost of primidone, it is usual to try patients on phenobarbitone or phenytoin first.

Toxicity.—Drowsiness to the extent of deep sleep from which the patient cannot be roused may occur for some hours, but patients usually adjust rapidly to the drug and tolerate it well. Primidone can be given with phenytoin, but when given with phenobarbitone it causes drowsiness.

N.H.S. Basic Price.—Tabs. 0.25 g., 100 for 16s. 10d.; oral suspension, 0.25 g. in 60 minims (3.5 ml.), 100 ml. for 5s. 8d.

APPROVED NAMES

The last supplement to the consolidated list of "approved names" was published in the *Journal* of August 8, 1959 (p. 918). A new supplement, dated September, 1959, is printed below. Communications relating to "approved names" should be addressed to the Secretary, British Pharmacopoeia Commission, General Medical Council, 44, Hallam Street, London, W.1.

Approved Name	Other Names	Notes
Ambutonium bromide	(3-Carbamoyl-3: 3-diphenylpropyl)ethyldimethylammonium bromide	Antispasmodic
Chlorthenoxazin	2-2′-Chloroethyl-2: 3-dihydro-4-oxobenz-1: 3-oxazine	Analgesic
Diamthazole ..	6-2′-Diethylaminoethoxy-2-dimethylaminobenzothiazole "Asterol" is the dihydrochloride	Antimycotic
Diethyltoluamide	*NN*-Diethyl-*m*-toluamide	Insect repellant
Dodicin	2: 5: 8-Triazaeicosane-1-carboxylic acid Dodecyl-di(aminoethyl)glycine	Antiseptic
Ethionamide ..	2-Ethyl*iso*nicotinthioamide	Antituberculosis agent
Flumethiazide ..	7-Sulphamoyl-6-trifluoromethylbenzo-1: 2: 4-thiadiazine 1: 1-dioxide	Diuretic
Guaiphenesin ..	3-*o*-Methoxyphenoxypropane-1: 2-diol Guaiacol glycerol ether "Respenyl"	Expectorant and antitussive
Haloperidol ..	4-*p*-Chlorophenyl-1-(3-*p*-fluorobenzoylpropyl)-piperidin-4-ol	Tranquillizer
Kanamycin ..	An antibiotic produced by *Streptomyces kanamyceticus* "Kantrex"	Antibiotic
Metahexamide ..	1-(3-Amino-4-methylbenzenesulphonyl)-3-*cyclo*hexylurea "Euglycin"; "Melanex"	Oral hypoglycaemic agent
Metformin ..	N^1N^1-Dimethyldiguanide	Oral hypoglycaemic agent
Methaqualone ..	2-Methyl-3-*o*-tolyl-4-quinazolone "Melsedin" is the hydrochloride	Hypnotic
Methazolamide	3-Acetylimino-4-methyl-2-sulphamoyl-1: 3: 4-thiadiazoline "Neptazane"	Treatment of glaucoma
Phenformin ..	N^1-Phenethyldiguanide "D.B.I."	Oral hypoglycaemic agent
Propyl docetrizoate	Propyl 3-diacetylamino-2: 4: 6-tri-iodobenzoate	Bronchographic agent
Proxyphylline ..	7-2′-Hydroxypropyltheophylline "Brontyl"	Similar to aminophylline
Sulphasomizole	5-*p*-Aminobenzenesulphonamido-3-methyl*iso*thiazole	Sulphonamide
Thioridazine ..	10-[2-(1-Methyl-2-piperidyl)-ethyl]-2-methylthiophenothiazine "Melleril" is the hydrochloride	Tranquillizer

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Leucocyte Agglutinins

Sir,—In your recent annotation on this subject (*Journal* August 29, p. 295) you make the final statement that leucocyte antibodies produced by foetal immunization of the mother do not seem to harm the foetus. This appears to be a broad and rather premature assumption. Our knowledge of the presence and frequency of leucocyte antibodies in the newborn is scanty, but we do know that scattered cases of neonatal neutropenia and agranulocytosis have been reported, and that some of these have proved fatal.[1 2] We have reported[1] two cases of neonatal neutropenia in siblings, and, while at the time no investigation for leucocyte antibodies was practicable, the work of Payne and Rolfs[3] makes it appear possible that such a mechanism may have been involved. Lehndorff[2] considers that his cases of acute neonatal neutropenia were examples of "allergy of the newborn" and postulated sensitization *in utero* followed by massive release of the antibody into the foetal circulation by rupture of chorionic villi during labour.

The syndromes of infantile familial neutropenia of the more chronic type,[4 5] and of acute neonatal infection where neutropenia is attributed to marrow depression by toxins, also seem to be worthy of investigation from this aspect before the possession of leucocyte antibodies in the neonatal period is accepted as a harmless condition.—I am, etc.,

Department of Pathology, University of Saskatchewan, Canada. H. E. Emson.

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5 Béguez César, A., *Bol. Soc. cubana Pediat.*, 1943, **15**, 900.

Tongue-tie

Sir,—May I congratulate Dr. I. M. Cullum on rediscoverjng tongue-tie and on his fascinating historical research (*Journal*, September 19, p. 497)? I regret that he did not consult that other repository of ancient knowledge, the textbook of anatomy,[1] from which he would have discovered that fatal tongue-swallowing can only arise from the separation of the genioglossi from the genial tubercles at the back of the mandible, and troublesome haemorrhage from the division of the terminal parts of the lingual arteries as they run to the tip of the tongue on either side of the frenulum. A guard was commonly attached to the old surgical dissectors[2] to protect these from surgical damage.

I feel the admission of these occasional babies for formal operation is unnecessary, as the frenulum can readily be separated from the back of the gum and jaw by firm pressure with the pulp of the finger. This procedure takes about two seconds and does indeed give immediate relief. Provided too much is not attempted, complications will not arise.—I am, etc.,

Rugby. S. C. Rogers.

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1 *Gray's Anatomy*, 27th edition, pp. 707 and 1290, London, 1938.
2 Bailey, Hamilton, and McNeill Love, R. J., *A Short Practice of Surgery*, 5th edition, p. 144, London, 1946.

Treatment of Pilonidal Sinus

Sir,—I was tempted last week to comment on an omission in the article by Mr. A. J. H. Rains (*Journal*, August 15, p. 171), and this week this became a definite decision when I noted the same omission in the letter written by Mr. D. Lang Stevenson (*Journal*, September 12, p. 430). This error is expressed in his statement that "leaving the resulting wound open to heal by second intention is common practice to-day, *no doubt because of lack of success with primary suture*." (My italics.) I cannot agree that he is correct in making this assumption.

Our surgical technique is not determined by mere expediency but by our conception of the pathological process involved and a consequent planned attempt to eradicate it. Surely the problems involved in the excision of an ellipse of skin and subcutaneous tissue down to periosteum, and the subsequent closure of the wound, with obliteration of dead space and primary union as its end result, are not peculiar to this area of the body. Twenty years ago I too was puzzled "to find the literature, year after year, implying that a problem exists." I am satisfied that it still exists, but the real problem is not that of securing primary union after excision of the sinus with its secondary abscess tracks, but that which is created by the reappearance of an exactly similar pilonidal sinus three, four, or five years later—after an undoubtedly sound primary union.

If one accepts the congenital theory of aetiology there should never be any late recurrences of this kind. If, on the other hand, one accepts the "hair trauma" theory, then it is clearly undesirable to aim once again at the approximation, in the midline of the natal cleft, of two skin edges which still grow hair sloping in opposing directions. Surgeons who accept this aetiology aim, as a matter of deliberate policy, at the production of a non-hairbearing cicatrix in the sacro-coccygeal midline. With skin grafting this is not an unduly lengthy procedure.—I am, etc.,

Douglas, Isle of Man. Eric Vernon.

Diabetes in the Tropics

Sir,—In the Diabetic Clinic for Zulu and Indian patients at the King Edward VIII Hospital in Durban, we are compelled on many occasions by force of circumstance (patient ignorance; through dislike of, or irregularity, of insulin injections) to adopt therapeutic measures which would probably not be regarded as good diabetic practice in non-tropical countries, in respect of the use of oral therapy. As many as 15% fall into this category of patients who would not ordinarily be regarded as suitable candidates for oral therapy, and some cases have features which would absolutely contraindicate the use of these drugs. Our task in changing these unlikely patients from insulin to oral therapy is frequently facilitated by the fact that patients, previously "dependent" upon insulin, will default from the Clinic and arrive back a few months later having had no treatment, though feeling fairly well, but with a heavy glycosuria and having lost a good deal of weight. Most of these patients have been Indians, and a good many of them thin.

The mildness of tropical diabetes is frequently stressed (*Journal*, January 24, p. 219), though previously we have noted (*Journal*, July 18, p. 73) that 7% of all our Zulu diabetics have been admitted in diabetic coma. We should, however, like to mention in detail certain established diabetics, who had previously been ketotic,

or who were or had been pregnant, or who belonged to the so-called "J" type of diabetes[1 2] whom we have been able to control satisfactorily with oral antidiabetic substances.[3 4]

In two "J" types, we achieved remarkable results; previously (*Journal*, July 18, p. 73) we had recorded disappointments trying to lower the dose of insulin in "J" types with oral therapy.

(*1*).—*Indian male, thin, "J" type, aged 39, 16-year diabetic on 160 units lente daily*: was very anxious to have a trial of "tablets" because of painful local reactions to insulin. Was changed to chlorpropamide, 250 mg. twice daily, and warned of risk; he has remained well controlled and almost free of sugar for four months, and feels very well.

(*2*).—*Indian male, thin, "J" type, aged 17, 3-year diabetic on 240 units lente daily*: suffering from "true" diabetic cataracts. Was put on to 250 mg. chlorpropamide twice daily and insulin dosage reduced to 100 units lente daily; developed five hypoglycaemic reactions in one week: encouraged by this, we dropped the insulin altogether, and he has been very well controlled, free of sugar, and quite well for three months and very grateful for not having to inject himself with large doses of insulin.

Pregnancy in the established diabetic is an absolute contraindication to oral therapy, though we have found it very useful in the "glycosuria of pregnancy."

(*3*).—*Zulu girl, thin, aged 19, 3-year diabetic on 40 units lente daily*: became pregnant, and at the 24th week became so lackadaisical about her insulin injections that she was put, in desperation, on to tolbutamide, 500 mg. t.d.s., and became perfectly controlled, virtually sugar free. Was delivered of a fine baby by caesarean section at the 36th week, in spite of having developed hypertension and albuminuria at the 32nd week. Four months after she is perfectly controlled on 500 mg. t.d.s.

(*4*).—*Zulu girl, thin, aged 27, pregnant, 4-year diabetic on 40 units lente daily*: two previous pregnancies under insulin "control" ended with stillbirths. Changed to tolbutamide, 500 mg. t.d.s., at 20th week, and was delivered of a live baby by induction at the 36th week, and at time of default two months later was controlled on oral therapy.

(*5*).—*Indian girl, thin, aged 26, 5-year diabetic on 20 units lente daily*: two stillbirths on insulin "control," and finally had live baby whilst on insulin. Very anxious to change to oral therapy, and was given a trial of tolbutamide with excellent control, and has been virtually sugar free for six months.

Previous ketosis or diabetic coma are a contraindication to the use of oral therapy.

(*6*).—*Zulu woman, thin, aged 46, admitted in diabetic coma initially*: made good recovery with energetic treatment and large doses of insulin. Six weeks after discharge was changed to tolbutamide at her own request, and was very well controlled for six months; then developed a severe cold, became ketotic, and had to be put on to insulin again.

In the diabetic nephropathy of the Kimmelstiel–Wilson type, the insulin requirements often fall in the later stages. We decided to try oral therapy in two cases, in spite of unchanging insulin requirements.

(*7*).—*Indian male, thin, aged 47, 16-year diabetic on 40 units daily*: classical advanced Kimmelstiel–Wilson nephropathy. Changed to tolbutamide 500 mg. daily, and developed hypoglycaemic symptoms, the nature of which he knew well, and which were reversed by sugar. Dose lowered to 250 mg. t.d.s. and he has been well controlled for five months thus far.

(*8*).—*Zulu male, thin, aged 44, 11-year diabetic on 60 units lente daily*: one of our two Zulus with Kimmelstiel–Wilson nephropathy. Changed to tolbutamide, 500 mg. t.d.s., with very good control for five months so far.

These are a few of the rather unusual results that we have achieved in our Clinic. In the last 400 diabetics that were referred to the Clinic, only 9 were put on to insulin. The majority of these 400 patients were fat middle-aged and young Indian patients and fat middle-aged Zulu patients, though we have had good results in a number of thin Indians, both female and male, who have been put on to oral therapy *as soon as the glycosuria has been noted*. We have not followed our patients long enough to draw any definite conclusions, but our results bear out the general mildness of the tropical diabetes, though this is by no means invariably so; there does seem to be a place for the use of oral treatment in the tropics for young thin diabetics, for pregnant diabetics, and for some of those patients who have been ketotic.

Our object in reporting these cases briefly is to find out whether other doctors (particularly in Jamaica) in the tropics and subtropics have had similar results with oral therapy.—We are, etc.

The Diabetic Clinic,
King Edward VIII Hospital,
Durban.

G. D. Campbell.
W. G. McNeill.

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4 Campbell, G. D., *The Zulu Diabetic*. Address at 1959 S.A. Medical Congress.

Sextuplets

Sir,—I believe that the literature relating to multiple births does not contain any well-authenticated record of a set of sextuplets. The accompanying photograph, which was found among the papers of the late Professor Sir Alexander Simpson, may therefore be of interest. The birth took place at Accra in 1903 to a woman called

Ashong, and the photograph was taken by a missionary in the area. The case was later reported to Sir Alexander in the following letter, dated February 3, 1905.

"Dear Dr. Simpson,

"I think this photograph may have some interest for you. A native woman on the Gold Coast had all those children at a birth. They were all living when born, but were allowed to die. When the photograph was taken by our friend Mr. Schultz of the Basil Mission, all were alive except the first on the right."

The event does not appear to have been reported previously in medical literature, although I believe it may have achieved mention in the daily press at the time. In accordance with native custom, which believed multiple births to be unlucky, this unique set were allowed to die, although it seems that five of them were in good condition after delivery.—I am, etc.,

W. T. Simpson.

Duncan Flockhart Research Laboratories,
Edinburgh, 11.

The Fossil Skull from Olduwai

SIR,—I have to-day, September 17, seen in our Kenya daily paper what purports to be an extract from the *British Medical Journal* (September 19, p. 487), criticizing my setting up of a new genus within the Australopithecinae for the new fossil skull from Olduwai Gorge. I am most surprised that a journal of the standing of the *British Medical Journal* should have allowed such comment before the publication of my scientific report on the specimen and of the detailed photographs. Whoever wrote your annotation refers to the "anatomical characters which may be perceived from the published photograph," but, at the time that was written, the *only* photographs of the specimen to have been published were of the palate only, whereas we have an almost complete skull.

Scientists who know my published work, both on fossil Suidae and on fossil Primates, know that I am usually accused of being too much of a "lumper," and it is a novelty for me to be accused of setting up a new genus without foundation. While I agree with your contributor that the "arbitrary multiplication of genera and species bedevils the study of fossil man," I can also assure him that I did not take the step of setting up a new genus without very great thought, and that I am sure that when he has seen all the evidence he will agree with me. I can only wish he had not rushed into unnecessary criticism before he had a chance to study the facts. By the time this letter reaches you, or very soon after, a clear statement of my reasons for setting up a new genus, together with photos of the skull, will have appeared in *Nature*.

On October 7, at 5 p.m., at the British Academy I shall lecture on the skull, and I invite your contributor to attend—as guest of the lecturer—to learn a few facts about the skull before he comments further.—I am, etc.,

The Coryndon Museum, Nairobi, Kenya. L. S. B. LEAKEY.

Thalidomide

SIR,—I have recently been using a new non-barbiturate sedative drug, "distaval" (thalidomide), to treat insomnia in elderly patients. It is claimed that this drug is non-toxic in that it does not produce untoward effects even if taken in large overdose. This claim is based on animal experimental work in which it proved impossible to determine a minimum lethal dose. In support of this work I would like to quote the following case from my own experience.

Mr. D., aged 70, had been taking 200 mg. of thalidomide nightly for insomnia associated with mild senile dementia. One evening he "got muddled" and took 21 tablets (2,100 mg.) by mistake. No specific treatment was given and he did not vomit. After 12 hours' apparently normal sleep, without evidence of respiratory or cardiac depression, he woke up, subsequently remaining a little drowsy for a further 24 hours.

I wonder if any other practitioners have had similar experiences of accidental or suicidal overdose with thalidomide, because it does seem that this drug is a satisfactory sedative and hypnotic in many patients, and on the above evidence its use might go a long way towards reducing the present annual mortality from overdoses of the central nervous system depressants currently prescribed.—I am, etc.,

Southampton. L. P. DE SOUZA.

Incidence of Intussusception

SIR,—The recent article by Professor Donald Court and Dr. George Knox (*Journal*, September 12, p. 408) once more notes the unknown aetiology of this disease. From observation and a wide reading, it has seemed to me that primary intussusception is a manifestation of Ogilvie's syndrome in the infant's small gut, the mesenteric lesion being the large inflamed lymph nodes invariably present throughout. And, to my mind, non-specific mesenteric adenitis is the same disease appearing in the more mature gut in older children. These latter have genuine recurrent colic. I have observed, and operated on at the request of various consultants, a series of 34 cases. The colic lasts 5 to 30 minutes, and in my opinion is due to intense spasm of the small gut and perhaps even to the more intense ischaemia of self-reducing intussusceptions, both of which have been observed at operation. The child cries, may be doubled up with pain or roll about with it. Immediately it passes off the child is back to normal—in fact, as is seen in biliary or renal colic. I used to see these cases frequently in Lancashire, but have seen very few here in Birmingham.

Perhaps the virologists could elucidate the cause of the lymphadenitis, as we know some viruses are associated with chronic enlargement of lymphoid tissue. In 75% the lymph nodes are "sterile."—I am, etc.,

Birmingham. F. V. A. BOSC.

Filtered Air

SIR,—A paper by Tchijevsky[1] has recently come to my notice describing the detrimental effects on experimental animals of breathing filtered air, the effects being ascribed to the exclusion or discharge of aero-ions by the filter, these ions being normally present in air in varying numbers and being considered by the author to play a vital part in oxidation processes in the body.

It appears that these effects are not produced if unfiltered air is breathed for even short periods each day. In considering the applications of these experiments to human medicine it seems to me that while a number of individuals, in industry and elsewhere, breathe filtered air for long periods, one of the few situations where such air may be taken continuously for weeks on end is in the case of a poliomyelitis patient with a cuffed tracheostomy tube in place, receiving positive-pressure respiration from a machine incorporating an air filter. While many machines do not include such a filter, there are some—e.g., the "Engström"—which do, and I would be most interested to hear from any clinician who has had the care of such a patient. In the animals the effects produced initially were intense lassitude, muscle weakness, loss of appetite, and loss of weight. Some or all of these are of course occasioned by the disease itself in the case of poliomyelitis patients, but, as in the reference quoted the mortality rate of the animals was 100% if the experiments were persisted with, the matter is clearly one of some importance.—I am, etc.,

The Western Hospital, London, S.W.6. P. H. BYLES.

REFERENCE

[1] Tchijevsky, A. L., *Acta med. scand.*, 1941, **106**, 516.

Carbon-monoxide Hazard at Altitude

SIR,—Dr. L. G. C. E. Pugh (*Journal*, January 24, p. 192) has reported on the carbon-monoxide poisoning hazard in members of the Commonwealth Trans-Antarctic Expedition. He showed that the poisoning was caused by partial combustion in the stoves, or by exhaust fumes, when the air supply was restricted as in the tents or the caboose. Pugh also pointed out that the hazard from carbon-monoxide poisoning is greater at altitude because the lowered atmospheric oxygen tension will reduce combustion and the lowered arterial oxygen saturation will result in more severe effects from a given blood concentration of carbon monoxide.

After Legrand and his colleagues had reported in 1945[1] an unexplained increase in carbon-monoxide blood levels in men exposed to oxygen deficiency, we carried out experimental studies[2 3] that showed a spontaneous increase in the blood alcohol and carbon-monoxide levels of subjects placed in atmospheres of low oxygen tension, as at high altitude. We suggested at the time that this might be due to an unusual anaerobic glycolysis (glucose → alcohol + carbon monoxide) caused by the lowered oxygen tension. The phenomenon in man would thus be comparable to the incomplete combustion in the stoves. Perhaps what was observed in the members of the Commonwealth Trans-Antarctic Expedition was also a consequence of this effect of altitude.—I am, etc.,

St. Thomas Hospital, Portogruaro, Venice. G. LEONARDI.

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"Tricking" the Patient

SIR,—There is one matter, arising out of the Podola case, which calls for comment and discussion in medical circles, and which, I feel, should be aired in your columns. What is "trickery" in a medical examination?

In the vast majority of examinations of patients by the vast majority of doctors, it is almost automatic for the doctor to believe and accept as true what the patient tells him. The reasons for this are obvious and self-evident. In examining a patient who is taking out an insurance life-policy, the doctor is not to be blamed if he does not so readily accept all statements about perfect health, and if he is prepared to assure himself to the best of his ability that this is so. Equally, if he is examining a man who complains of a host of illnesses that he may *not* be medically passed (for example, a conscript for National Service), a doctor is expected not to accept every statement at its face value. Thirdly, if a patient complains of apparent organic disorders, whereas the doctor feels it may be a hysteria case, the doctor may employ such methods and techniques in his examination as he considers suitable to help ascertain the truth. All experienced doctors are well aware of all this. Is this trickery? It is, indeed, part of the education and training of medical students and young doctors to learn just how to try to find out the truth, often despite the patient. Textbooks are full of descriptions of how to conduct innumerable such tests.

I should have thought that to convince a patient he needed an operation merely in order to receive a large fee would be trickery, and base trickery indeed. I should have thought that to give a patient the wrong medicine (if dispensing oneself) deliberately, because one did not possess the correct one at the moment, would be again base trickery. Trickery may be possible in treatment, although I do not know of any such. But trickery in examination? What does it mean?—I am, etc.,

Reigate, Surrey. S. SHARMAN.

Psychiatry for the G.P.

SIR,—The National Association for Mental Health is aware of the keen interest among general practitioners in mental-health problems, and of the important contribution which they can and do make in the prevention and treatment of mental illness, and have therefore felt that they would welcome an opportunity of considering current treatments in psychiatry and new developments in the mental-health field. With this in view the Association has arranged a residential week-end course to take place in London from November 13 to 15, 1959, at which the following lecturers have agreed to take part: Dr. Desmond Curran, Dr. H. V. Dicks, Dr. J. J. Fleminger, Dr. T. F. Main, Dr. Felix Post, Dr. W. Linford Rees, Dr. H. J. Shorvon, and Dr. C. A. H. Watts.

Your readers may like to know that further particulars may be obtained from the Education Secretary, National Association for Mental Health, 39, Queen Anne Street, London, W.1. (Telephone Welbeck 1272.)—I am, etc.,

London, W.1. T. P. REES.

"Scotch-on-the-Rocks"

SIR,—There is a method of drinking Scotch whisky known as "Scotch-on-the-Rocks." Neat whisky is poured on ice cubes and sipped as an aperitif.

I have experience of one case of leukoplakic glossitis in a man who did not smoke tobacco but who had been drinking in this manner for 18 months. The typical white patches on the sides of the tongue, and all his symptoms, disappeared within two weeks of following my advice to put more water with it. His tongue is now normal.—I am, etc.,

Bangor. W. SKYRME REES.

POINTS FROM LETTERS

Control of Plague

Dr. L. F. HIRST (Begbroke, Oxford) writes: In your issue of September 12 there is a leading article on the control of plague (p. 415). Foci of wild rodent plague are said to be sylvatic. In my *Conquest of Plague* (p. 193), I urge that the term campestral ought to be used instead of the term sylvatic. Field rodent or wild rodent plague is a disease of the plains of the South African veldt, of Southern Russia, the South American pampas, the Western States of U.S.A., Kenya, and Uganda. When plague spread in East Anglia in 1906–10 it was a disease of the fields. The term sylvatic implies that the disease is in the woods.

Early Radiological Reports Wanted

Dr. E. R. N. GRIGG (Box 293, Champaign, Illinois, U.S.A.) writes: For the purpose of a paper, I am collecting information on *x*-ray reports—i.e., those somewhat ephemeral texts in which the radiologist lists and interprets the findings elicited during diagnostic *x*-ray examinations. I would particularly like to receive originals of *x*-ray reports dated prior to 1910, or more recent ones if signed by renowned radiologists. Incidentally, does anybody know who wrote the first *x*-ray report? Original *x*-ray reports, after being photographed, will be returned to their sender, to whom due acknowledgment will be made in the event of publication.

Obituary

RIPLEY ODDIE, B.M., Ch.B.

Dr. Ripley Oddie, medical consultant and director of Bayer Products Ltd., and formerly an assistant editor of the *British Medical Journal*, died at his home in London on September 20 after a long illness. He was 57 years of age.

Ripley Oddie was born on May 18, 1902, the son of Dr. S. Ingleby-Oddie, the well-known coroner of the Westminster district of London. From Rugby School he went on to Oriel College, Oxford, and then to St. Thomas's Hospital. Having graduated B.M., Ch.B. in 1927 he was first house-physician, then senior resident medical casualty officer, and finally chief assistant in the skin department at St. Thomas's.

Oddie joined the staff of the *B.M.J.* as a sub-editor in 1931. Before then he had had some experience in popular medical journalism, and was for a period medical correspondent to the *Daily Mail*. Oddie was one of two medical sub-editors under Dr. N. G. Horner as editor. They both spent a great deal of time in preparing manuscripts for the press, almost to the extent of rewriting, on occasions, articles appearing in the front part of the *Journal*. This was a task performed according to the standards laid down by Horner's predecessor, Sir Dawson Williams. After he left the *B.M.J.* to edit, for a time, the popular house organ of Bayer Products Ltd., he used to say that the *B.M.J.* training stood him in good stead, if only for the reason that he had not been taught even the elements of punctuation at school. For a time he edited the "Epitome of Current Medical Literature" which made up the end pages of the *B.M.J.* before this section was replaced by the "Key to Current Medical Literature"—both forerunners of the now separately published *Abstracts of World Medicine*.

Oddie was an engaging character and a cheerful and entertaining colleague. He got a lot of enjoyment out of life. Though he found the routine work of sub-editor on the *B.M.J.* far more exacting than he had expected, and far more time-consuming, nevertheless his decision to leave was not taken light-heartedly, and the regret he felt at this was most firmly shared by his colleagues.

He joined Bayer Products Ltd., as medical adviser in 1935, just at the time when "prontosil," the first of the sulphonamide drugs, was being put on the market. He remained with that company for the rest of his life, though during recent years ill-health prevented him from working in a full-time capacity. Shortly after the outbreak of the second world war he joined the Royal Air Force Volunteer Reserve and was quickly promoted to wing commander. He was the first editor appointed by Sir Harold Whittingham in 1941 to collect and edit material for the history of the medical services of the R.A.F. during the second world war, and the foreword to the first volume of the official history paid tribute to his devoted labours. He had to relinquish his commission because of ill-health at the end of 1943.

Ripley Oddie suffered grievously in the last few years of his life. In addition to the trials of chronic illness he fell and fractured his hip about a year ago. But despite this he managed to maintain his interest in all the things he regarded as important, and he continued to pursue his historical research into that corner of Chelsea in which he lived.

In his younger days he was a skilful and elegant games-player, particularly tennis (the real variety) and golf, and like his wife, formerly Jeannette Kessler, he was a good skier. An acute observer and critic, and outstandingly perceptive, he had a sharp eye for the ludicrous in much that went on around him, even to the end. He met the tribulations of his last illness with great courage.

G. D. writes: When I first met Ripley Oddie he had already been a very sick man for several months, and what struck me immediately was his unforced gaiety and his unaffected lack of concern about his harsh disability. It was, it seemed, a bit of a bore, best ignored: there were other things. There was not only *Ulysses* to be read, but every word of commentary that had been written about it; there were long, carefree letters to be composed for his friends, notebooks to be filled with day-to-day jottings about his innumerable lively interests. There were good wines, smoked salmon, strawberries, and good conversation. Escapism? Yes, if it be so to wrap in soft blankets against the cold until it is no longer noticed. At all times he was the "compleat" clubman, warm, urbane, and debonair. Even when, during his convalescence, he would come slouching back in his shabbiest clothes from one of his bird-watching expeditions, this patrician quality was almost laughably manifest.

I happened to be visiting him when he had his first stroke, which occurred while he was still recovering from his second-stage thoracoplasty he had undergone three weeks previously. So ingrained was his habitual courtesy as a host that, dazed and aphasic as he was, he kept apologizing for his mental dishevelment, and floundered in his bed to press cigarettes on his guest and to locate an ashtray. I have never met anyone who ran so true to form, the form of a slightly bygone and better-mannered age. A most lovable "clubbable" man.

R. O. M. E. writes: Although we at Bayers had known for a long time that Dr. Oddie was a very sick man, the news of his death came as a very great shock and brought a feeling of personal loss. A quiet man, "R. O.," as he was affectionately called in the office, was greatly liked by all who worked with him. He took great pride in *Clinical Excerpts*, and it is a tribute to his objective reporting that this publication, alone among house journals, appeared throughout the last war as a scientific publication with the approval of the Paper Controller. Dr. Oddie's contribution to the building of the company's good reputation was this very regard for factual and scientific objectivity. With his fellow directors he was always congenial and co-operative, and during the 24 years he was with us he was invariably considerate and courteous to his staff, ever willing to advise or help any of us who went to him with a personal problem. "R. O." had his own very special brand of humour, at times slightly sardonic but never spiteful, and one always left his office with a happy grin or a chuckle—it was a delight to work with him. We shall long remember him as a very kindly man, with a great sense of responsibility to his company and to the profession, but, above all, as an example of the very best type of English gentleman.

ABRAHAM FLEXNER, M.D.(Hon.), LL.D., Litt.D.

Dr. Abraham Flexner, director-emeritus of the Institute for Advanced Study at Princeton, died on September 20 at the age of 92. The report which he wrote fifty years ago about medical schools in the United States was a landmark in the history of medical education.

Abraham Flexner was one of nine children born to parents who came to the United States from Bohemia. His brother Simon was the famous bacteriologist and director of the Rockefeller Institute of Medical Research. Abraham Flexner, after graduating at Johns Hopkins, founded his own highly successful school at Louisville in 1891, and after some years he was able to take his master's degree at

Harvard and to study at a number of universities in Europe. By this time his fame as an educationist had grown, and he was invited by the Carnegie Foundation for the Advancement of Teaching to investigate the medical schools in the U.S.A. and Canada. After visiting 155 of them he produced in 1910 his famous report "Bulletin Number Four" for the Carnegie Foundation. He said later about this, "I struck from the shoulder, naming names and places." Not only did he describe the chaotic state of medical education at that time but he outlined a programme of reconstruction which, so great was the impact of his report, was rapidly put into effect. Nearly half of the existing schools were shut down, and during subsequent years the quality of the teaching at the remaining schools, and of the doctors which they turned out, was vastly improved. Flexner followed up "Bulletin Number Four" with a report entitled "Medical Education in Europe."

In 1917 he became a member of the General Education Board of the Rockefeller Foundation, and thereafter he was remarkably successful in persuading philanthropists such as John D. Rockefeller and J. B. Morgan to donate large sums of money towards improvements in medical education. Describing the technique by which these improvements were financed, he wrote: "The Rockefeller organization estimated in one school after another what was needed. It offered one-third, sometimes one-half, provided the institution raised the balance. In the course of ten or twelve years the situation was transformed." But in 1957 he saw things slipping back. "The situation to-day is bleak," he wrote. "Practically every medical school in the country is in the red . . . there is an estimate that an additional income of ten million a year is needed for eighty-two schools."

An associate member of All Souls, Dr. Flexner was Rhodes Memorial lecturer at Oxford and also Taylorian lecturer. The Princeton Institute for Advanced Study, which was his own creation, was opened under his directorship in 1930.

Dr. Flexner received honorary medical degrees from the Universities of Berlin and Brussels, and other distinctions from universities all over the world. Three years ago he was presented with the third Lahey award, sponsored by the American Medical Association, the Association of American Medical Colleges, and the National Fund for Medical Education.

W. F. RAWSON, M.R.C.S., F.R.C.S.Ed., F.R.C.O.G.

Mr. W. F. Rawson, formerly obstetrician and gynaecologist to St. Luke's Hospital, Bradford, died at his home at Bradford on August 15 at the age of 87 years.

William Foster Rawson, who was born on August 4, 1872, was the son of a general practitioner who practised in the Thornton district of Bradford. From Thornton Grammar School he went on to study medicine at Leeds, qualifying in 1895. He then entered into partnership, but found time for study and was admitted a Fellow of the Royal College of Surgeons of Edinburgh in 1901. In the same year he was appointed honorary assistant surgeon to the Bradford Royal Infirmary. This appointment he resigned in 1903, since he found the hospital claims on his time incompatible with an extensive general practice.

Mr. Rawson remained in general practice until he was appointed visiting obstetrician and gynaecologist to St. Luke's Municipal General Hospital (the first municipal hospital in the country) in December, 1921, an appointment he held until the early days of the second world war. In 1925, when he was chairman of the Bradford Division of the B.M.A., he served as vice-president of the Section of Obstetrics and Gynaecology at the Annual Meeting of the B.M.A., held that year in Bradford. He was elected F.R.C.O.G. in 1936.

G. W. T. writes: Mr. Rawson was a charming man, quiet and unassuming, and took a keen personal interest in those with whom he worked, many of whom he helped in various ways. He not only opened the door for the charlady, but insisted that she preceded him through it. The work of his hospital increased rapidly and he had the satisfaction of seeing the new obstetric unit completed before he retired. Increasing deafness isolated him during his latter years, and he outlived most of his colleagues and friends, but his kindliness is still vividly remembered in the hospital. He leaves a widow and two daughters.

EDWARD NEWTON PRICE, M.R.C.S., L.R.C.P. D.A.

Dr. E. Newton Price, anaesthetist to the Hastings group of hospitals, died very suddenly at his home at St. Leonards-on-Sea on August 23, a few days after his 63rd birthday.

Edward Newton Price served throughout the first world war as a combatant officer and was severely wounded. After the war he studied medicine at St. Mary's Hospital, London, qualifying in 1927. After holding the resident post of house-physician at his teaching hospital he went into general practice in Bournemouth for a time before settling in St. Leonards-on-Sea in 1937. He combined a private general practice there with work as a specialist anaesthetist, in the first place as honorary anaesthetist to the Royal East Sussex Hospital, and, having taken the D.A. in 1942, as specialist anaesthetist to the Hastings group of hospitals at the inception of the National Health Service, a post which he held up to the time of his death.

A colleague writes: Eddie Newton Price had a most likable personality and was well loved by his patients, whom he treated with scrupulous care. He was a skilled and reliable anaesthetist who never fussed. He never sought the limelight, being a diffident man, but he was always excellent company, with a pawky sense of humour and a fund of anecdotes. An accomplished linguist, he spoke both French and German fluently. In his home life he was exceedingly happy, and we offer our deep sympathy to his widow and only son.

D. H. GEFFEN, O.B.E., M.D., D.P.H.

The obituary of Dr. D. H. Geffen was published in the *Journal* of September 26 (p. 583).

Dr. SUSAN TRACY writes: Those of us who knew Dennis Geffen well will remember him best not as an able and experienced administrator, lecturer, and medical officer of health, but as a kindly, sympathetic doctor ready to listen to and help those who consulted him. His advice was always practical and full of common sense. He never lost his interest in clinical medicine, and was glad that so many of his staff and friends came to him, not only about their own ailments, but also those of their families. He was especially interested in children and young people, and lost no opportunity of meeting them and learning their point of view, and he followed the careers of his many young friends with genuine interest. He was proud of the part he had taken in the growth of the maternal and child-welfare services in this country, and often commented on the improvement in the last decade in the health of babies and children. Of the many articles and books which he wrote, it was those on maternal and child welfare that gave him greatest pleasure and satisfaction.

Enthusiastic and hard-working, he never spared himself, and even on holiday would lose no opportunity of studying the health services of the country in which he was at that particular moment. His greatest interest was in his work, but he had a sound knowledge and appreciation of pictures and works of art, and possessed a fine collection of early Italian bronzes and majolica. In his youth he had been a keen amateur musician, enjoying mainly opera and classical music.

Dr. Geffen will be mourned by many of all ages who knew him as a very good friend and wise counsellor on whom they could always rely, but they will know that he

died, as he would have wished, when he could no longer work. Essentially a family man, he and his wife loved to entertain the younger members of their family, both in their London home and in the country, and latterly some of his happiest times were those spent with his own grandsons. Our deepest sympathy is extended to his widow, sons, and all the members of his family.

Medico-Legal

FITNESS TO PLEAD

[From our Legal Correspondent]

It is as repugnant to any canon of civilized conduct as it is to the idea of crime and punishment that a man should stand his trial if he is not in a fit state of mental health to understand what is going on at his trial and to make his defence. When there is a doubt whether a prisoner is in such a state the matter is raised on arraignment before he pleads "Guilty" or "Not Guilty" to the indictment. A jury is then empanelled to try as a preliminary issue whether he is "fit to plead"—that is, in a fit state of mental health to understand what is going on at his trial and to make his defence.

It has generally been thought that whether a man is "in a fit state to make his defence" for this purpose means whether he is in a state of mind at the trial to enable him to give his lawyers sensible instructions.

Podola Trial

When the matter was raised at the Podola trial it was raised on the basis that, if Podola was suffering from a genuine amnesia, whether hysterical or not, he could not give his lawyers instructions on which his defence could be made. This raised the question whether instructions that he could remember nothing were sensible instructions or not. If that is all a prisoner can do, is he in a fit state to make his defence?

The Podola trial is the first occasion on which this problem has been canvassed. As a necessary preliminary, the jury had to decide whether Podola was genuinely suffering from amnesia or not, and it was to that point that the evidence was directed. Since the jury found that he was not, it was unnecessary for the judge to decide and to direct the jury whether genuine amnesia which deprived the prisoner of all recollection of what happened at the material time rendered him "unfit to plead." The point remains open for future decision and it will no doubt be raised again.

It is a startling proposition at first sight that someone who at his trial is wholly sane and in full possession of his powers of communication may nevertheless be unfit to plead by reason of loss of memory, and it would be an attractive means of escape to detention at Her Majesty's Pleasure from something worse. On the other hand, to convict and punish someone for doing something he can remember nothing about involves philosophic difficulties. The solution is not helped by the fact that no appeal lies from the jury's decision one way or the other on whether a prisoner is fit to plead. Judges of assize will have to struggle with this problem unaided by their collective wisdom expressed through the Court of Criminal Appeal.

Plastic Bags.—Within two days and only 12 miles apart, two Lincolnshire men, aged 23 and 43, were found dead with plastic bags over their heads. The Cleethorpes coroner recorded a verdict of suicide while of unsound mind in the case of the elder man, and of accidental death in the case of the younger. There was no evidence at the inquests to suggest that the deaths were in any way connected.—*Yorkshire Post*, August 10 and 12.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 12** (No. 36) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	6	6	1	0		3	0	1	0	
Dysentery	414	47	181	5		316	36	135	11	11
Encephalitis, acute	6	0		0		1	0		0	
Enteric fever:										
Typhoid	9	3	0	2		5	0	1	0	1
Paratyphoid	20	1	1 (B)	0		9	1	0	1	1 (B)
Food-poisoning	291	34	18	2		275	30	17	1	
Infective enteritis or diarrhoea under 2 years				23					16	32
Measles*	848	32	22	13		1,977	118	17	20	21
Meningococcal infection	6	1	14	3		10	0	13	0	
Ophthalmia neonatorum	19	1	4	1		22	3	3	0	
Pneumonia†	107	6	96	1		141	9	105	1	
Poliomyelitis, acute:										
Paralytic	26	4	0	} 1		{ 60	1	} 20	1	3
Non-paralytic	12	2	4			{ 20	1			
Puerperal fever§	220	28	17	0		188	19	12	0	1
Scarlet fever	303	16	62	27		304	19	55	7	8
Tuberculosis:										
Respiratory	424	52	58	15		412	44	91	13	
Non-respiratory	54	6	17	3		73	4	12	3	
Whooping-cough	695	50	176	9		791	45	100	61	6

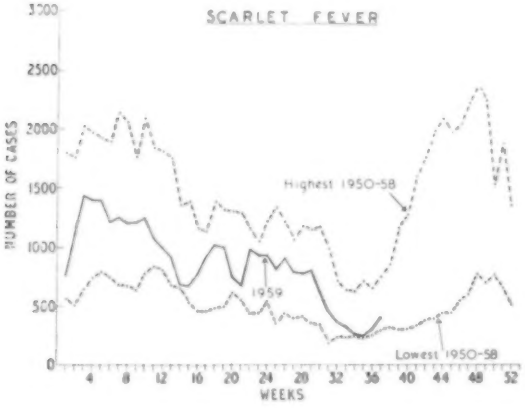
DEATHS	1959,					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	1	0	0	6	0	1	0	0
Influenza	4	1	0	0	1	4	0	1	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	326	26	6	5	5	340	26	12	8	3
Poliomyelitis, acute	5	2		0	0	4	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	} 56	{ 4	5	0	0	} 70	{ 7	8	1	1
Non-respiratory		{ 1	0	0	0		{ 0	0	0	0
Whooping-cough	2	0	0	0	0	0	0	0	0	0
Deaths 0–1 year	274	20	17	8	12	284	19	23	4	8
Deaths (excluding stillbirths)	7,947	635	430	103	134	7,878	622	477	79	141
LIVE BIRTHS	13,811	1216	938	259	370	13,658	1116	961	191	361
STILLBIRTHS	309	33	20			323	26	19		

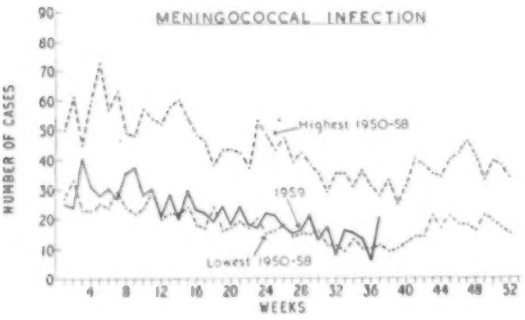
* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

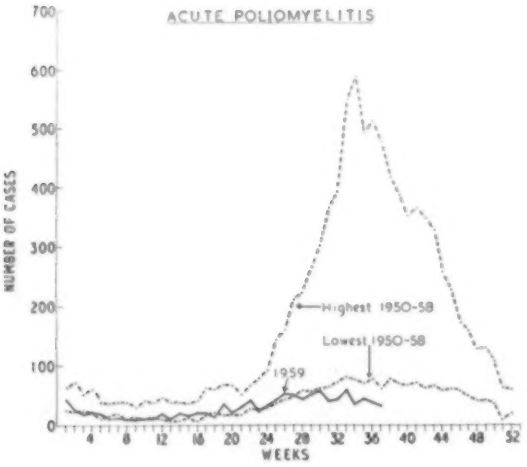
Vital Statistics

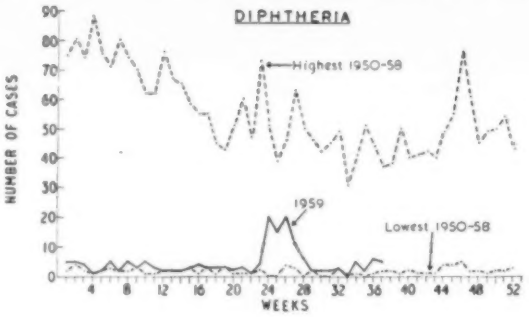
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending September 19

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Sept. 12	Week Ending Sept. 19
Acute Poliomyelitis		
London	6	**9**
Essex	3	**4**
Hampshire	5	**3**
Lancashire	5	**4**
Meningococcal Infection		
Warwickshire	1	**8**
Birmingham C.B.	1	**8**
Dysentery		
Lancashire	65	**92**
Liverpool C.B.	18	**37**
London	47	**42**
Staffordshire	6	**27**
Bilston M.B.	0	**23**
Warwickshire	41	**40**
Coventry C.B.	26	**33**
Yorkshire East Riding	28	**19**
Kingston upon Hull C.B.	16	**17**
Yorkshire West Riding	61	**74**
Barnsley C.B.	21	**24**
Bradford C.B.	11	**11**
Leeds C.B.	19	**25**
Glasgow	137	**145**
Dundee	12	**28**
Paratyphoid Fever		
Caernarvonshire	6	**5**
Caernarvon M.B.	5	**4**
Lancashire	6	**4**
Manchester C.B.	1	**3**
Food-poisoning		
Lancashire	69	**97**
Blackpool C.B.	17	**14**
Liverpool C.B.	20	**29**
Diphtheria		
London	6	**3**
Finsbury	6	**3**
Continued Fever		
Glasgow	0	**5**
Acute Infectious Encephalitis		
Durham	4	**2**
Gateshead C.B.	4	**2**
Leicestershire	0	**4**
Barrow upon Soar R.D.	0	**3**
Blaby R.D.	0	**1**

Medical News

Arsenical Haulm Destroyers.—Because of the dry weather the Ministry of Agriculture, Fisheries and Food has strongly advised potato-growers to postpone lifting the crop for as long as possible after arsenic has been sprayed so that the contaminated vegetation has a better chance of dying and breaking down or of being cleansed by rain. Whenever possible potato-pickers should wash their hands and faces before eating, drinking, or smoking. The handling of potato plants sprayed with arsenic within 10 days of the spraying is forbidden by law unless the workers wear overalls, rubber gloves, rubber boots, and dust masks.

Welwyn-Hatfield General Hospital.—The foundation stone of the new Welwyn-Hatfield General Hospital was laid on September 22 by the Minister of Health, Mr. D. Walker-Smith. The chairman of the North-West Metropolitan

Regional Hospital Board, Lord Cottesloe, said that it was one of the first new hospitals with any substantial number of beds to be embarked on since the war. The building, a plan of which is shown here, will cost £1,530,000, and the main part will be completed in 1962. Warm-coloured traditional materials will be used in the eight-story building, which will have 11 wards with 324 beds, and a 100-bed annex for psychiatric patients. Mr. Walker-Smith welcomed this feature of the hospital as a means of relieving the stigma which may be attached to mental illness.

Health of the Army.—The report of the Director-General, Army Medical Services, for 1955 begins with the welcome news that delay in publication of this annual report is to be reduced in future. The present volume shows a satisfactory state of health in the Army. Of 221,354 persons called up for service in any of the armed Forces, 64% were fully fit for service and 14% were entirely unfit. The Army had to take a rather larger share of the partially fit than did the other Services. Among these is a group characterized as "poor doers." They usually lack confidence and are of poor physique. Special conditioning courses for these men have proved successful, over 90% being restored to their units fully fit. Morale was maintained at a high level "despite the publicity given to the complaints of a vociferous and disgruntled minority." But morale was not high among three-year regular soldiers, most of whom had been attracted to soldiering not by inclination "but by the immediate financial benefits." Again, among officers "morale was apt to decline in those short-service commissioned captains and majors whose futures were insecure, and whose commitments were increasing yearly without any relative improvement in their prospects."

Leverhulme Trust Fund.—The Trust has issued a brief report which simply classifies the awards, amounting to £854,358, which have been made during the first 25 years of its activities from 1932 to 1955. Future reports, which it is hoped to issue triennially, will give chapter and verse. Broadly speaking, the report says, the lion's share of the fund goes to the furtherance of research in the universities, teaching hospitals, and other centres of higher education, since it is these, in the long run, which are likely to produce the most fruitful results. Universities and centres of higher education have enjoyed £179,400 of the sum mentioned, medical research £115,300, and the learned societies and research institutions £84,000.

Sterilizing by Irradiation.—The United Kingdom Atomic Energy Authority has announced that a pilot plant for testing irradiation processes, such as the sterilization of medical equipment and the disinfestation of packaged products, is being built for operation at the end of this year. The new plant is being built at the Wantage Radiation Laboratories for the Technological Irradiation Group of the Isotope Research Division, Atomic Energy Research Establishment. It will occupy an area of about 10,000 sq. ft., of which roughly 1,000 sq. ft. is taken up by the irradiation cell itself with its massive concrete shielding walls. To make full use of the source, which is continually radiating and decaying, the plant will operate 24 hours a day, and in this period of time three tons of medical products or imported animal fibres can be rendered sterile. Interlocks and control devices will be incorporated to prevent injury to the workers and to ensure the correct radiation dosage.

"Biochemical Journal."—Dr. A. G. Ogston, F.R.S., has resigned from the chairmanship of the *Biochemical Journal's* editorial board and Dr. W. V. Thorpe has been appointed as his successor. Correspondence and communications should still be sent to the secretary to the Editorial Board, Lister Institute of Preventive Medicine, Chelsea Bridge Road, London, S.W.1.

Chairmanship of Food Standards Committee.—Mr. R. Groves is to serve as chairman of the Food Standards Committee, Ministry of Agriculture, Fisheries, and Food, for a period of three years. He is a member of King's College Hospital Medical School Council.

University of St. Andrews.—Dr. J. S. S. Stewart has been appointed to a lectureship in surgery in Queen's College, Dundee.

Professor L. J. Witts has been invited to give the Francis Shepherd Memorial Lecture in Montreal on October 5.

COMING EVENTS

Leeds Neurological Sciences Colloquium.—A series of free weekly lectures will be held on Tuesdays at 5.15 p.m., Littlewood Hall, General Infirmary, Leeds. Details will appear in the *Journal* Diary each week.

International Congress of Gastroenterology.—Leyden, April 20–24, 1960. Details from the Secretariat of the Congress, 16, Lange Voorhout, The Hague, the Netherlands. Lectures by October 1.

Institute of Dermatology.—Semi-permanent exhibitions are available during the winter course. The first, from October 5 to 26, will be by Dr. H. Haber on "Histology of Normal Skin."

National Varicose Foundation Silver Medal.—The subject of this year's essay competition for the newly endowed medal is "The Cause and Care of the Post-thrombotic Leg." Entries must be received by April 30, 1960, but intending entrants should write to the Secretary of the Foundation, 5, Park Lane, Wembley, Middlesex, for further details.

Muscular Dystrophy Group.—New address: 26, Borough High Street, London, S.E.1 (HOP 2324).

Liverpool University.—A course of eight lectures on "Epilepsy," Wednesdays, beginning October 14, 8–9.30 pm., University Main Building, Brownlow Hill. Details from Director of Extra-Mural Studies, 9, Abercromby Square, Liverpool, 7.

Harveian Oration.—Sir Russell Brain: "William Harvey, Neurologist," October 19, 3 p.m., Royal College of Physicians, Pall Mall East, London, S.W.1.

Institute of Basic Medical Sciences.—Course in Genetics, Statistics, and Radio-isotopes, October 19–21. Details from Mr. W. F. Davis, Secretary of the Institute, Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2 (HOL 3474).

Association of Anaesthetists of Great Britain and Ireland.—Annual Meeting: October 22 and 23, Stratford-upon-Avon. Details from the honorary secretary of the association, 47, Lincoln's Inn Fields, London, W.C.2.

St. Thomas's Hospital Old Students' Dinner.—Savoy Hotel, London (entrance, Victoria Embankment), October 29, 7 p.m.

U.C.H. Medical School.—The annual dinner of past and present students will be held at the Savoy Hotel on October 30. Tickets (36s. each) from the Hon. Secretary, Old Students' Association, U.C.H. Medical School, University Street, London, W.C.1. Postgraduate demonstrations will be held at the school and hospital earlier in the day. The A.G.M. of the Old Students' Association will be at 5 p.m. on October 29.

Leeds School of Medicine Annual Dinner.—The 69th annual dinner of past and present men students of the school will be held at the Griffin Hotel on October 30, 7 p.m. Tickets (price 27s. 6d.) from the Hon. Secretary, Dinner Committee, School of Medicine, Thoresby Place, Leeds, 2.

Wessex Rahere Club.—The Autumn Dinner will take place at the Lansdown Grove Hotel, Bath, on Saturday, October 31. Membership of the Club is open to all Bart's men practising in the West Country. Further details will be circulated on request to members and to any other Bart's men who are interested by Mr. A. Daunt Bateman, 3, The Circus, Bath.

St. John Ambulance Brigade Surgeons' Conference.—The Conference will be held at B.M.A. House, Tavistock Square, London, W.C.1, on October 31 and November 1. Details from Surgeon-in-Chief's Department, 8, Grosvenor Crescent, London, S.W.1.

Glasgow University and R.F.P.S.(Glas.).—Specialist conference: "The Thyroid Gland and its Diseases," in the Faculty's Hall, 242, St. Vincent Street, Glasgow, C.2, November 11–13. For details see *Journal* advertisement page 64.

NEW ISSUES

British Journal of Venereal Diseases.—Issued quarterly (£3 annually). The new issue (Vol. 35, No. 2) includes:

Editorial.
Ankylosing Spondylitis. R. M. Mason.
Significance of Sacro-Iliitis in Reiter's Disease. George W. Cronka.
Reiter's Disease and Ankylosing Spondylitis. J. K. Oates.
Bacteriological and Biochemical Investigations in Reiter's Syndrome. George W. Cronka.
Incidence of Genital Infection in Male Patients with Ankylosing Spondylitis. J. K. Oates.
Pelvic Infection as a Cause of Bilateral Sacro-Iliac Arthritis and Ankylosing Spondylitis. Ronald G. Grainger and C. S. Nicol.
Reiter's Disease. Hamilton Bailey and W. J. Bishop.
Treatment of Venereal Disease Outside the Hospital Service.
Syphilis of Bones. A. J. King and R. D. Catterall.
Specificity and Sensitivity of the Reiter Protein Complement-Fixation (RPCF) Test. J. H. Bekker.
Book Reviews.
6 Canadian Symposium on Non-Gonococcal Urethritis.
Abstracts.

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SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, October 6

Institute of Neurology.—5.30 p.m., Professor Clinton N. Woolsey (U.S.A.): Organization of Somatic Sensory and Motor Areas of the Cerebral Cortex.

Leeds Neurological Sciences Colloquium 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Sir Francis Walshe, F.R.S.: What we have to Unlearn about the Anatomy and Physiology of the Nervous System.

Wednesday, October 7

Institute of Dermatology.—5.30 p.m., Dr. R. W. Riddell: Tinea and Moniliasis.

Institute of Diseases of the Chest.—5 p.m., Dr. F. Lee Lander: Asthma.

Institute of Urology.—4.30 for 5 p.m., Dr. W. N. Mascall: Gonococcal Urethritis.

Manchester Medical Society.—At Physiology Theatre, Medical School, Manchester University, 4 for 4.30 p.m., Presidential Address by Dr. C. E. Sykes: Modern Anaesthesia.

Royal College of Surgeons of England.—5 p.m., Hunterian Lecture by Professor R. G. Robinson: Hydatid Disease affecting the Nervous System.

Yorkshire Society of Anaesthetists.—At Leeds General Infirmary, 8.30 p.m., Dr. A. Crampton Smith: Some Experiences with Physical Methods in the Treatment of Chest Infections.

Thursday, October 8

Institute of Dermatology.—5.30 p.m., Mr. A. T. Gray: Ointment Bases.

Institute of Neurology.—5.30 p.m., Professor J. Z. Young, F.R.S.: Nature of Living Memory Stores.

● London Hospital Medical College.—At Bearsted Theatre, 4.30 p.m., Schorstein Memorial Lecture by Sir Russell Brain, Bt.: Neurological Tradition at the London Hospital.

London Jewish Hospital Medical Society.—At Medical Society of London, 8.30 p.m., Presidential Address by Professor John Yudkin: Rations and Irrationality.

North-Western Thoracic Society.—At Clinical Sciences Building, York Place, Manchester, 5 p.m., Presidential Address by Dr. Eric Smith: Chest Diseases in Biblical Times.

Royal College of Surgeons of England.—5 p.m., Gordon-Watson Lecture by Mr. L. E. C. Norbury: Gordon-Watson and St. Mark's Hospital.

St. George's Hospital Medical School.—5 p.m., Dr. Desmond Curran: demonstration in psychiatry.

● West London Medico-Chirurgical Society.—At Rembrandt Hotel, S.W., 7.30 for 8 p.m., Presidential Address by Dr. Eric Hudson: Every Physician Almost, Hath His Favourite Disease.

Friday, October 9

● Institute of Dermatology.—5.30 p.m., Dr. H. J. Wallace: clinical demonstration.

Institute of Diseases of the Chest.—5 p.m., Radiological demonstration by Dr. B. Strickland.

Institute of Neurology.—4.45 p.m., Dr. J. A. V. Bates: Electrode and the Neurosurgeon.

King's College Hospital Medical School.—At Medical School Lecture Theatre, 4.30 p.m., 12th Thomas Percy Legs Memorial Lecture by Sir Clement Price Thomas: Carcinoma of the Lung.

Society of Medical Officers of Health: Metropolitan Branch.—At Society's Committee Room, Tavistock House South, W.C., 2.30 p.m., Dr. A. J. H. Tomlinson: Bacteriology To-day.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bartlett.—On September 21, 1959, at Bristol, to Anne (formerly Cousins), M.B., Ch.B., wife of Charles Bartlett, F.R.C.S., a brother for Alice, Jane, and Catherine.

DEATHS

Davis.—On August 30, 1959, at 6, Glisson Road, Cambridge, Pamela Elizabeth Davis, M.B., B.Chir., aged 36.

Fry.—On August 8, 1959, in Australia, Henry Kenneth Fry, D.S.O., M.D., D.P.H.

Kolapore.—On August 29, 1959, Framroze Jamsetjee Kolapore, M.R.C.S., L.R.C.P., Lieutenant-Colonel, I.M.S., retired.

McIvar.—On August 30, 1959, at Parkholm Military Hospital, Chester, John William Allan McIver, M.B., Ch.B., Colonel, R.A.M.C., retired.

Mathers.—On August 27, 1959, at a Dunfermline hospital, James Alexander Mathers, L.R.C.P.&S.Ed., L.R.F.P.S., of Saline, Fife, formerly of Dunkeld.

Middlebrook.—On August 26, 1959, at a Bournemouth nursing-home, Annie May Middlebrook, M.B., Ch.B.

Rowe.—On August 22, 1959, at 62, Earlsway, Chester, John Mary Rowe, O.B.E., *M.C.*, M.B., Ch.B.

Sammon.—On August 18, 1959, at 6, Suffolk Street, Helensburgh, Dumbartonshire, John Douglas Sammon, M.B., Ch.B., D.M.R.T.

Sheare.—On August 21, 1959, in hospital, Marguerite Stanton Sheare, M.B., B.S.

Shuter.—On August 28, 1959, at 6, Chiswick Lane, London, W., George Percy Shuter, M.B., B.Ch., D.P.H.

Slim.—On July 27, 1959, at Crossways, Bittadon, near Barnstaple, Devon, Kathleen Mary Slim, M.B., Ch.B.

Southan.—On August 24, 1959, at 110, Regent Road, Leicester, Percy Southan, L.S.A., L.M.S.S.A., aged 82.

Sutcliffe.—On August 27, 1959, at White House, Grundisburgh, Suffolk, William Francis Sutcliffe, M.R.C.S., L.R.C.P.

Waller.—On August 21, 1959, at 77, Carlisle Mansions, London, S.W., Louis Waller, L.M.S.S.A.

Weber.—On August 10, 1959, at St. Bartholomew's Hospital, London, E.C., Henryk Weber, M.D., of 40, Bracewell Road, London, W.

Whyte.—On August 13, 1959, at Musgrave Clinic, Belfast, Joseph Norris Whyte, M.D., D.P.H.

Young.—On July 29, 1959, in Johannesburg, S. Africa, Alfred Ernest Young, O.B.E., M.R.C.S., L.R.C.P., L.D.S. R.C.S., late of Basutoland Medical Service, aged 68.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Sarcoidosis

Q.—*Have there been any recent advances in the knowledge of the aetiology and differential diagnosis of sarcoidosis?*

A.—The aetiology of sarcoidosis remains a matter of controversy. The hypothesis that it is related in some way to tuberculous infection has recently received some support from the claim of Strawbridge[1] to have isolated mycolic acid from sarcoid lesions. This work, however, has been criticized on the ground that the identification of the mycolic acid is uncertain. Cummings,[2] of the United States Veterans Administration, has reported some observations which he claims connect pine pollens with sarcoidosis. The basis of these is in the main epidemiological, and much further work is required before the significance of this work can be evaluated. These two much-disputed contributions constitute the only new approaches made recently to this problem. Diagnosis continues to depend upon the recognition of one of the many clinico-radiological syndromes of the disease supported by histological evidence, the degree of support required varying inversely with the confidence with which the clinical picture is recognized. The Kveim test suffers from the defect that it depends entirely upon the availability of a reliable antigen. The difficulty of securing this is very great, so that it cannot be considered as a practicable routine test for general use.[3]

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1 Nethercott, S. E., and Strawbridge, W. G., *Lancet*, 1956, **2**, 1132.
2 Cummings, M. M., and Hudgins, P. C., *Amer. J. med. Sci.*, 1958, **236**, 311.
3 Israel, H. L., Sones, M., Beerman, H., and Pastras, T., *New Engl. J. Med.*, 1958, **259**, 365.

Nasal Staphylococcal Carriers

Q.—*In trying to reduce staphylococcal infection of operation wounds in hospital, is anything to be gained by nasal swabbing of staff? Should carriers be taken off duty? Should they be treated, and, if so, how?*

A.—If facilities permit, and if preventable staphylococcal infections are occurring in patients, nasal swabbing of the staff is advisable, but only if the examination goes beyond the mere detection of carriers, which are likely in any case to be numerous, and includes either phage typing or at least determination of antibiotic sensitivities. Experience has shown that the most dangerous strains are those resistant not only to penicillin and usually streptomycin but to the tetracyclines. Carriers of such strains or of any staphylococcus which can be identified as the cause of an outbreak may be taken off duty if there are few of them, if the situation is serious, and particularly if it is also found that they are extensive skin carriers dispersing the organism freely. The most effective treatment known is the application to the nose of a cream containing bacitracin and neomycin: the carrier should also regularly use a soap containing hexachlorophene.

Diagnosis of Hypoglycaemia

Q.—*What are the best methods of diagnosing recurrent attacks of hypoglycaemia causing fainting, etc.? Is the six-hour glucose tolerance curve diagnostic?*

A.—The best method of establishing a causal relationship between attacks of "fainting" and hypoglycaemia is to estimate the blood sugar during an attack. This, however, is rarely possible, and an effort must therefore be made to determine the blood-sugar level at those times of day at which such attacks are most apt to occur; in practice these are likely to be in the fasting state or from two to four hours after a meal. The prolonged, or six-hour, glucose-tolerance test often gives useful information both in cases of true hyperinsulinism and in so-called functional hypoglycaemia, but a negative result cannot be regarded as conclusive evidence against the diagnosis. The importance of exercise as a factor in producing attacks cannot be ignored, and in the diagnosis of islet tumour the following procedure may prove of value. The patient has no food overnight and blood is collected hourly from 9 a.m. to 2 p.m.; during this period the patient takes no food, but exercises moderately. In functional hypoglycaemia it is rarely necessary to carry the curve beyond four hours, but, in order not to miss a transient fall in blood-sugar level, estimations should be carried out at intervals of not longer than 30 minutes.

Drinking-glasses and Infection

Q.—*Is there any evidence that drinking-glasses, when used again quickly after ordinary washing and drying, may act as vehicles of infection?*

A.—The answer depends on what is meant by "ordinary" washing and drying. What would be ordinary in a private house, which is washing in clean water and drying with a dry, clean cloth, would probably remove at least 99.99% of bacteria from a smooth glass surface. On the other hand, common practice in less sanitary catering establishments, whether restaurants or merely public houses, consists in swilling a glass in a sink or other receptacle containing water which has previously been soiled by large numbers of others, and "drying" it with a cloth which may by that time be frankly wet with this variously contaminated water. Examination of such water has shown that its bacterial content may be very high indeed, and may include pathogenic species. Actual proof that colds, influenza, streptococcal sore throats, and Vincent's infection are transmitted in this way is obviously almost impossible to obtain, but ascertained facts about the degree of contamination of such glasses leave no doubt that it can occur. The danger can of course be overcome by the addition of suitable disinfectants and detergents to the washing-water and its sufficiently frequent renewal before the activity of these reagents has been exhausted.

Penicillin Sensitivity

Q.—*What is the technique for testing patients for sensitivity to penicillin? In cases of sensitivity, what is the technique for desensitization?*

A.—The technique for testing sensitivity to penicillin depends on the type and degree of sensitivity. For suspected contact dermatitis the patch test is used and for the anaphylactic type of reaction the conjunctival test and/or the skin test, by the scratch or prick method, followed when negative by the intracutaneous method. The dosage cannot be standardized, since the degree of sensitivity varies very widely. There is the risk of severe and even dangerous reactions from even very small doses in the acutely sensitive, and there is general agreement that a negative test, even with accepted correct techniques and dosage, does not rule out clinical sensitivity. The dosage and procedures for desensitization also vary widely and again carry risks. It must be emphasized that these procedures should only be carried out by experts.

In very sensitive patients severe reactions may occur even with a strength of 10 units,[1] and in an extreme case occurred after 0.000003 unit of penicillin intracutaneously.[2] A reasonable strength to start with intracutaneously might be 5 units, then 100 units, and occasionally 500 units, in 0.1 ml., after a negative prick test. Smith[3] used a strength of 300,000 units of procaine penicillin per ml. for both scratch and conjunctival tests in 1,365 patients, and only had one constitutional reaction. For intracutaneous testing after a negative scratch test, Nilzen[4] recommends 0.02 ml. of a

strength of 100 to 1,000 units of benzyl sodium or potassium penicillin (but not the procaine), and Tuft *et al.*[5] recommended 0.02 ml. of a strength of 10,000 units, but advocated control tests with the vehicle used in the penicillin preparation.

Patch testing is only occasionally necessary, since the patient has already had the equivalent of a patch test. If necessary, a patch test with the penicillin ointment previously used by the patient may be done. Peck *et al.*[6] used for patch testing a strength of 2,000 and 10,000 units; Kern and Wimberley[7] used 50,000 units; and Hopkins and Lawrence[8] used 100,000 units. Smith[9] gave 600,000 units of procaine penicillin to 778 patients immediately after negative conjunctival and prick tests, and had one constitutional reaction. Nilzen[4] found an apparent failure rate of 10%.

Desensitization is usually carried out only when contact with penicillin can hardly be avoided, as in nurses and doctors. It is usually carried out in hospital, and the initial dose should be that which just gives a positive intracutaneous skin reaction or just fails to give a reaction (often carried out under cover of an antihistamine or cortisone). Favourable results have been recorded.[9] Alexander[10] used an initial dose of 50 units three-hourly intramuscularly and doubled the dose every day, if no reaction, until a dose of 200,000 units could be taken without reaction. Others[4] have used very much smaller doses subcutaneously (when a local reaction can be seen and subsequent dosage altered). Nilzen points out that the treatment requires much time and is considerably more difficult to carry out than pollen desensitization.

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Venous Ulceration

Q.—*What is the accepted current treatment of varicose ulceration?*

A.—This type of ulceration, better named venous ulceration, since varicose veins are frequently absent and often unimportant, has a complex aetiology, and the question cannot be answered adequately in a short space. One of the monographs on the subject should be consulted.[1–3] In the treatment of these ulcers the patient as a whole must be considered.

The essential cause is chronic oedema of the leg resulting from poor venous return following breakdown of the "leg muscle pump." The rhythmic contractions of the calf muscles during walking squeeze the blood in the deep veins upwards, the valves in these veins preventing its return in the opposite direction. The commonest cause of a defect in this pumping mechanism is thrombophlebitis of the deep veins. The superficial veins, even though varicose, play little part. Although surgical treatment of the superficial veins may benefit a few selected patients, in the majority it is not helpful. Cockett's operation on the perforating veins may be useful. The deep venous system is affected and nothing, at present, can be done surgically to put this right once the valves have been destroyed by thrombophlebitis and the ensuing process of recanalization.

A venous ulcer cannot be healed until the oedema is abolished. This is best achieved by the use of elastic compressive bandages, though, in addition, postural drainage with the leg raised above the level of the heart for an hour daily is helpful. Massage may also be used to lessen oedema, especially when there is much induration, but elastic support is required in addition. Elastic compression from the toes to the knee may be obtained by elastic adhesive or elastic webbing bandages. Elastic crêpe bandages rarely give enough compression. If the patient's leg is irritated by elastic adhesive bandages, a soothing cotton bandage impregnated with ichthymol may be applied under it. It is rarely necessary to treat the patient in bed—only when the ulcer is large and unhealed for many years. Local treatment is of minor importance, and even foul ulcers are usually healed readily merely by eliminating the oedema. If Gram-negative organisms are present, and if the tissues around the ulcer are inflamed, antiseptics or antibiotics may be applied, but none which are notorious as sensitizing agents (such as penicillin, streptomycin, and chloramphenicol). Oxytetracycline dihydrate and polymyxin ointment is useful, and so is 2% of phenoxyethanol in Lassar's paste.

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3 Foote, R. R., *The Physical Treatment of Varicose Ulcers*, 1958. Edinburgh and London.

Poliomyelitis Vaccination and Multiple Sclerosis

Q.—*Is it advisable to immunize against poliomyelitis a woman aged 35 years who is 6 months pregnant and who has multiple sclerosis at present quiescent?*

A.—There is no evidence at all that poliomyelitis vaccine has any effect in reactivating disseminated sclerosis, nor would one expect it to have. On the other hand pregnant women appear to be specially susceptible to poliomyelitis, and the patient should be immunized without delay.

Prevention of Seasickness

Q.—*What drug or drugs do you recommend to prevent seasickness during a voyage of 24 hours' duration?*

A.—The best drug to prevent seasickness during a voyage of 24 hours' duration is hyoscine (or scopolamine), the adult dose being 0.6 mg. of hyoscine hydrobromide. It is efficient, it acts in half an hour, and it does not cause depression. It does not take away appetite, though it causes dryness of the mouth. Its cost is minimal, about 3d. for 10 tablets. Antihistamine substances are far more expensive, and none of them are entirely free from sedative effects. Cyclizine, dimenhydrinate, and meclozine are all recommended for children, the dose for age 8 being one-half the adult dose.

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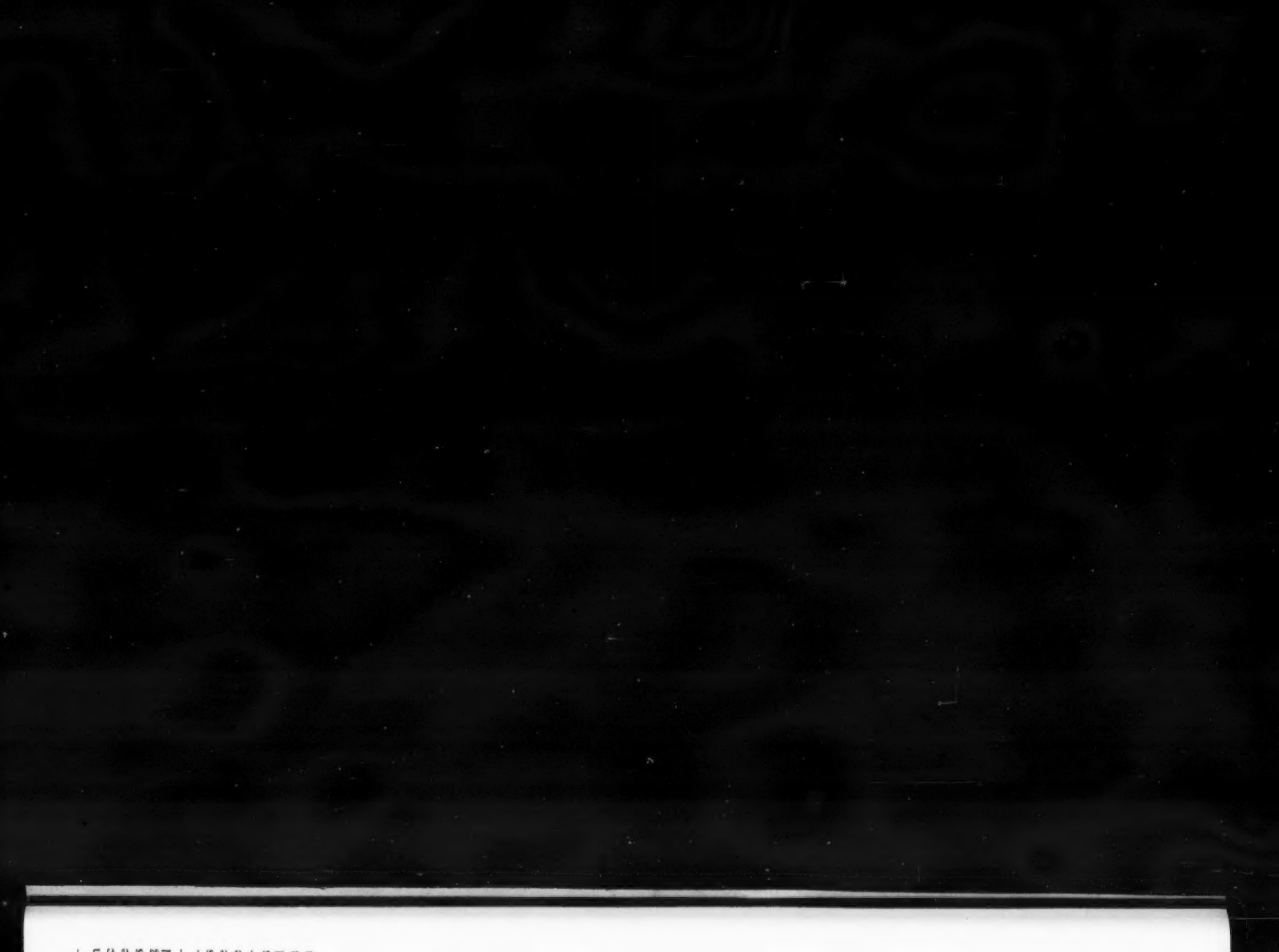
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